Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Pro98-04

Regulatory Proposal

Postapplication Exposure Monitoring Test Guidelines

The purpose of this Regulatory Proposal is to solicit comments from stakeholders on the harmonized Postapplication Exposure Assessment Guideline.

Under the Regulatory Capacity Building Subcommittee of the North American Free Trade Agreement (NAFTA) Technical Working Group (TWG) on Pesticides, the United States Environmental Protection Agency (EPA), Health Canada's Pest Management Regulatory Agency (PMRA) and the California Department of Pesticide Regulation are developing a harmonized Postapplication Exposure Assessment Guideline. It will be based on the draft EPA *Series 875 - Occupational and Residential Exposure Test Guidelines - Group B - Postapplication Explsure Monitoring Test Guidelines*. The purpose of the document is to provide harmonized guidance in designing and implementing studies required to assess postapplication exposure.

The PMRA Canada will work with the EPA to address all comments from stakeholders. As well, the PMRA will ensure that Canadian specific references and issues are incorportated into the document. This process will culminate in the release of a harmonized Postapplicatin Exposure Assessment Guideline.

Comments should be provided by October 22, 1998, to the Publications Coordinator at the address listed below.

(publié aussi en français)

September 4, 1998

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Series 875 - Occupational and Residential Exposure Test Guidelines

Group B - POSTAPPLICATION EXPOSURE MONITORING TEST GUIDELINES

Version 5.4

U.S. Environmental Protection Agency
Office of Prevention, Pesticides,
and Toxic Substances

February 10, 1998

DISCLAIMER

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ABOUT THE REVISION

WHAT IT IS:

Series 875 - Group B: *Postapplication Exposure Monitoring Guidelines* is a revision and expansion of the former *Pesticide Assessment Guidelines Subdivision K*. Series 875 - Group B is one of several guidelines available to assist the regulated community in designing and implementing studies required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

WHO IT'S FOR:

- Pesticide registrants and other individuals interested in postapplication exposure monitoring.

WHAT'S NEW:

These guidelines greatly expand the scope and depth of the existing Subdivision K Guidelines. Highlights include:

- Guidance on providing a study design;
- Guidance on conducting indoor/residential exposure monitoring;
- Guidance on conducting lawn/turf exposure monitoring;
- Guidance for providing detailed use information; and
- Guidance for providing detailed quality assurance and quality control data.

ORGANIZATION OF THIS DOCUMENT:

This document is divided into four Parts followed by an appendix. The actual "how-to" instructions are provided in Part B. Part A provides background material; Part C provides information on quality assurance and quality control; and Part D provides information on the calculations needed to assess exposure and risk.

FOR FURTHER INFORMATION CONTACT:

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UNITS OF MEASURE

cm	centimeter
gal	gallon
K	degrees Kelvin
kg	kilogram
L	liter
lb	pound
m	meter
mg	milligram
mL	milliliters
Pa	pascal
ppm	parts per million
%	percent
Torr/mm Hg	millimeters of mercury
μg	microgram
μm	micrometer

ACRONYMS

AChE	Acetyl Cholinesterase
ADD	Average Daily Dose
AEL	Allowable Exposure Level
ARC	Ambient Reentry Concentration
a.i.	Active Ingredient
ARTF	Agricultural Reentry Task Force
CBI	Confidential Business Information
COM	Consumer and Occupational Model
CFR	Code of Federal Regulations
DFR	Dislodgeable Foliar Residue
EPA	Environmental Protection Agency
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	The Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
HEAST	EPA's Health Effects Assessment Summary Tables
HED	Health Effects Division
HVAC	Heating, Ventilation, and Air Conditioning
GI	Gastrointestinal
GLPs	Good Laboratory Practices
IRIS	EPA's Integrated Risk Information System
ISR	Indoor Surface Residue
LADD	Lifetime Average Daily Dose
LC50	Median Lethal Concentration
LD50	Median Lethal Dose
LOD	Limit of Detection
log K_{ow}	Octanol/water Partition Coefficient
LOQ	Limit of Quantification
MCCEM	Multi-chamber Concentration and Exposure Model
MOE	Margin of Exposure
NIST	National Institute of Standards and Technology
NOAA	National Oceanic and Atmospheric Administration
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NOPES	Nonoccupational Pesticide Exposure Study
OECD	Organization for Economic and Cooperative Development
OP	Organophosphorous insecticides
OPP	The Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
ORETF	Outdoor Residential Exposure Task Force
PCP	Pentachlorophenol
PUF	Polyurethane Foam

ACRONYMS (continued)

QA	Quality Assurance
QA/QC	Quality Assurance/Quality Control
QAU	Quality Assurance Unit
QC	Quality Control
RDL	Reentry Dose Level
REI	Restricted-entry interval
SAP	FIFRA Scientific Advisory Panel
SCIES	Screening Consumer Inhalation Exposure Software
SRD	Soil Residue Dissipation
SVOCs	Semi-volatile Organic Chemicals
TC	Transfer Coefficients
TGAI	Technical Grade of the Active Ingredient
TSCA	The Toxic Substances Control Act
UAR	Unidentified Analytical Response
USDA	United States Department of Agriculture
VOCs	Volatile Organic Chemicals
WBD	Whole Body Dosimeters
WPS	Worker Protection Standards

PART A

BACKGROUND

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PART A - OVERVIEW AND SUMMARY

PREAMBLE

This publication, Series 875 - Occupational and Residential Exposure Test Guidelines Group B - Postapplication Exposure Monitoring Test Guidelines [formerly Subdivision K of the Pesticide Assessment Guidelines (U.S. EPA, 1984)] provides guidance to persons required to submit postapplication exposure data under 40 CFR 158.390. Generally, such data are required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) when certain toxicity and exposure criteria have been met. The data are used to determine restricted-entry intervals for agricultural applications, postapplication entry restrictions at non-agricultural sites, or whether a pesticide could be used without appreciable postapplication risk in residential settings.

The postapplication exposure guidelines are being revised because the existing guidelines (i.e., Subdivision K) no longer meet the needs of persons required to submit postapplication exposure data under FIFRA. When the Subdivision K guidelines were first published in 1984, they were designed to establish an acceptable scientific approach to the postapplication (i.e., reentry, which is the entry into a site subsequent to pesticide application) data requirements for typical agricultural exposure scenarios. Since 1984, there have been a number of changes in the U.S. Environmental Protection Agency's (EPA's) data needs and requirements. First, as a result of the reregistration process[1], the Agency has been requiring more postapplication studies. These include both occupational and residential postapplication studies. Second, there is currently little guidance available on conducting residential postapplication studies, and standardized methods for assessing risk from pesticide use in the home are needed. Third, the revisions to the Good Laboratory Practice Standards in 1989 have focused more attention on quality assurance and quality control (QA/QC). The Rejection Rate Analysis (U.S. EPA, 1993) indicated that the most common cause for rejection of studies was inadequacy or lack of QA/QC.[2] Please note that the revised guidance will harmonize, to the extent possible, with guidance issued by international organizations such as the Organization for Economic and Cooperative Development (OECD).

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[1] Reregistration is the Office of Pesticide Programs' process for reexamining supporting scientific data, reassessing human health and environmental risks, and making reregistration decisions for all pesticides initially registered before November 1, 1984.

[2] The Rejection Rate Analysis was undertaken to determine the reasons for study rejection and to help improve the acceptability rate of studies submitted for reregistration by pesticide registrants.

Initiatives to Generate Data

Two industry-wide proprietary Task Forces have been formed to share in the cost of developing generic exposure data to support pesticide product reregistrations in the United States, California, and Canada. Subject to further evaluation when data are completed, it is intended that the data generated by the Task Forces may also satisfy certain new product registration data requirements. The task force approach to fulfilling exposure data requirements has the potential to provide the Agency with a more complete and scientifically sound basis than is currently available for evaluating exposure at agricultural or residential use sites, including turf.

The *Agricultural Reentry Task Force (ARTF)* has been organized to develop a generic agricultural reentry exposure database intended to address agricultural postapplication and reentry data requirements for dermal and inhalation exposure (Guidelines 875.2400 and 875.2500). Proprietary studies will be evaluated for inclusion in the database, and data gaps will be identified in postapplication exposure data for agricultural uses. The ARTF will then conduct postapplication exposure studies and develop generic dermal transfer coefficients to cover hand labor activities for which insufficient data may exist.

The *Outdoor Residential Exposure Task Force (ORETF)* has been organized to develop exposure data for both professionals and non-professionals (residents) who mix, load, and apply pesticides to residential lawns or turf (Guidelines 875.1100 and 875.1300) and exposure data on non-professionals who reenter residential sites (grass lawn or turf) after pesticide application (Guidelines 875.2400 and 875.2500). As described above for the agricultural reentry database, existing published and proprietary studies will be evaluated for inclusion in the outdoor residential exposure database, and data gaps will be identified in both mixer/loader/applicator and postapplication exposure data for outdoor residential uses. The ORETF will then conduct mixer/loader/applicator and postapplication exposure studies and develop generic exposure data to support residential uses for which insufficient data may exist.

The proprietary generic agricultural and residential exposure data developed by the ARTF and the ORETF will be used in conjunction with product specific information (dislodgeable foliar residue data, toxicology data, etc.) to conduct risk assessments on a product-by-product basis, as needed.

A HISTORICAL PERSPECTIVE

Soon after the introduction of the organophosphorus (OP) insecticides in the late 1940s, specific toxic effects peculiar to some OP compounds were sometimes observed in field workers after applications of OP insecticides. These episodes were quite erratic; that is, the same pesticide might be used, at the same rate, on the same piece of ground, on the same crop for several years without any evidence of toxic effects, but in a subsequent year, a number of field workers might experience symptoms characteristic of OP poisoning. This made it very difficult to investigate the problem and contributed to a number of misconceptions. Among these misconceptions were the ideas that only inhibitors (i.e., OP and carbamate insecticides) of the enzyme acetyl cholinesterase (AChE) cause reentry problems, that exposure primarily occurred by inhalation, and that only acute effects occurred (Popendorf and Leffingwell, 1982).

Because it was difficult to obtain information about the conditions leading to a reentry episode, it was difficult to arrive at a realistic model for the derivation of reentry intervals (reentry intervals are now known as restricted-entry intervals). Several models/methods were proposed, but prior to 1980 an "epidemiological" model was the primary method for the establishment of restricted-entry intervals. For example, in the June 25, 1975, Federal Register (Vol 40, no. 123, p. 26900), it was stated: "A number of sporadic episodes of acute adverse effects in field workers have been ascribed to toxic levels of pesticide residues on plant surfaces....... Establishment of reentry intervals for a specific pesticide-crop-cultural practice combination is currently conceived as a two-step process: (1) postulating a reentry interval; and (2) testing the postulated interval in the field." This approach was not satisfactory to the Agency. At a meeting of the FIFRA Scientific Advisory Panel (SAP) on February 22 and 23, 1980, the Agency presented a new model for the establishment of reentry levels and restricted-entry intervals. This "Allowable Exposure Level" (AEL) model obviated the epidemiological method. It allowed the establishment of reentry levels and intervals from toxicity and dissipation data through the use of a correlation of "dislodgeable residue" levels with exposure levels. This method addresses any class of compound and any mode of toxicity whether the effect is acute or chronic. It also makes it possible to establish reentry levels and intervals without the exposure of individuals to possibly hazardous pesticide residue levels. In this version of Series 875 Group B, the AEL concept has been modified and redefined as the Reentry Dose Level (RDL).

The 1980 guideline draft was revised in response to public comment and SAP advice, and was presented to the SAP again in May 1981. The 1981 draft was again revised, presented to, and reviewed by the SAP as part of the publication of several guideline sections. The final version of Subdivision K was published in October 1984. The data discussed in Subdivision K were then codified as data requirements at 40 CFR 158.140. This present document is a revision and expansion of the existing Subdivision K (i.e., U.S. EPA, 1984). These guidelines build on the previous version; for estimating the restricted-entry interval, and add new areas for data requirements.

EVIDENCE OF POSTAPPLICATION EXPOSURE

Agricultural

There is nationwide concern over postapplication exposure to pesticides, both in the agricultural and residential environments. Concerns from exposure to agricultural pesticides first began to be raised during the 1950s and 1960s as many of the environmentally persistent organochlorine insecticides (generally of low acute toxicity) began to be replaced with less persistent, but often acutely toxic, compounds. Among such chemicals are parathion and other cholinesterase-inhibiting organophosphates and N-methyl carbamates, including phosalone, dialifor, and methomyl. As this transition to more acutely toxic pesticides occurred, workers entering treated fields to cultivate or harvest crops were, on rare occasions, subjected to exposures at levels capable of producing illness or even death (CDFA, 1987; Milby et al., 1964; Lores, et al., 1978; Krook et al., 1971; Coye et al., 1986).

Over the past 20 years, these occupational safety concerns have led to the development of a number of State and Federal programs for farmworker protection, including establishment of restricted-entry intervals for acutely toxic pesticides and those suspected of teratogenic or carcinogenic potential. While these programs have undoubtedly contributed to a reduced occupational pesticide exposure, the concerns have not been eliminated, as evidenced by continuing documentation of exposure and injury even in States, such as California, which have comparatively advanced exposure and safety standards (Maddy et al., 1990).

EPA estimates that there are approximately 2.25 million agricultural workers nationwide. Of this population, roughly 10,000 to 20,000 may suffer from acute pesticide poisoning annually (U.S. EPA, 1992a). In California during 1990, a total of 1,919 occupationally-related possible, probable, or definite pesticide poisonings were reported to the California Department of Pesticide Regulation.[3] Of these cases, 165 (about 8 percent) can be attributed to field exposure. From 1982 to 1988, such cases rose from 274 to 492 reported annually (CDPR, 1993).

Maddy et al. (1990) describes three separate incidents during 1987 in the Central Valley of California where 78 field workers harvesting grapes developed moderate to severe cholinesterase depression. Forty-seven (~60 percent) reported symptoms compatible with cholinesterase poisoning. Fourteen workers were hospitalized for periods ranging from 1 to 7 days. In another incident (Napa Valley), nine workers developed signs and symptoms consistent with cholinesterase poisoning. From all evidence gathered, it appears that the insecticide phosalone was the cause in all four episodes (Maddy et al., 1990).

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[3] Under State law (Section 2950 of the California Health and Safety Code), all California physicians are required to report any illness or injury suspected of having been caused by pesticide exposure.

Residential

Indoor Residential Exposure. Historically, concerns associated with the use of pesticides have focused primarily on agricultural environments. However, in recent years the use of pesticides in indoor and residential environments has escalated, initiating a cause for increased attention to pesticide exposures in these environments.

It is estimated that over 90 percent of United States households use a variety of pesticide products from antimicrobial disinfectants to insecticides (Godish, 1985). Research Triangle Institute (RTI, 1992) estimates that in 1990 about 20 percent of all households (about 16 million households) had their homes commercially treated for indoor pests such as cockroaches, ants, or fleas. This large percentage of pesticide usage warrants attention because most individuals spend a significant period of time indoors. It is estimated that on a daily basis an employed adult spends about 15 hours per day at home and a small child spends about 21 hours per day at home (Lewis, 1990).

According to the National Center for Health Statistics (NCHS, 1982-1991), residential pesticide poisoning resulted in 97 accidental deaths between 1980 and 1988. This accounts for approximately 77 percent of the pesticide deaths for which location was specified. Between 1981 and 1990, an annual average of 20,000 pesticide exposures were reported to emergency rooms throughout the United States (Blondell, 1990). Approximately 82 percent of these reportedly occurred in the home.

Another concern has been expressed about exposures to preservatives (i.e., antimicrobials) found indoors. Antimicrobial pesticides are used indoors to treat surfaces/areas/objects including, but not limited to, carpets, hard surfaces, floors, tables, laundry, mattresses, plastic products, etc. Another consideration is the exposure to volatile pesticide compounds contained in products used indoors (i.e., preservatives used in paints) for varying periods of time.

As a result of increased concern and lack of knowledge regarding the residential use of pesticides, EPA conducted the Nonoccupational Pesticide Exposure Study (NOPES), which measured residents' exposure to 32 pesticides. The study demonstrated that air levels of many pesticides were significantly higher indoors than outdoors (U.S. EPA, 1990). Currently, EPA is conducting the National Human Exposure Assessment Survey (NHEXAS), which will measure pollutant concentrations, including pesticides, in air, water, soil, dust, food, surfaces, and human tissues using various sampling techniques (Sexton et al., 1995a, 1995b). The survey will also collect human activity and population characteristic data via questionnaire. Some of the objectives of NHEXAS are to document the occurrence, distribution, and determinants of total exposure in the general population, monitor geographic and temporal trends in exposure, and evaluate factors that contribute to total exposure (Lebowitz et al., 1995).

Outdoor Residential Exposure. Each year, approximately 70 million pounds of pesticide active ingredients are used in the home and garden (LCPAC, 1993; GAO, 1993). According to the National Home and Garden Pesticide Use Survey (RTI, 1992), approximately 18 million households use pesticides on lawns, 8 million use pesticides on food crops, and 14 million use pesticides on ornamental plants. Approximately 15 percent of the 66.8 million households with private lawns have pesticides applied by someone other than the household member (i.e., a commercial lawn care company) (RTI, 1992). These statistics have generated considerable public concern over potential exposure and health effects, especially for children entering recently treated areas.

Outdoor-applied pesticides may also be tracked or transported indoors where they become a secondary source of exposure to the building occupants. Secondary sources of indoor exposures may occur from homeowner or commercially-applied lawn products (herbicides, insecticides, and fungicides); garden pesticides; agricultural or community spray drift; and fungicide-treated lumber. Transfer of lawn pesticides to indoor carpets by foot traffic was experimentally demonstrated by Nishioka et al. (1996). Pesticides are also used on playground equipment and in swimming pools (i.e., biocides) to which children may potentially be exposed (i.e., work clothing washed with other clothing, children touching contaminated clothing, etc.).

Children's Exposure. As a follow-up to the NOPES Study, EPA conducted a study to evaluate monitoring methods that may be used to assess potential exposures of children to pesticides found in the home environment. The study suggested that pesticides in household dust and yard soils may represent a source of exposure among infants and children. The study sampled homes that were not specifically treated with pesticides for the purposes of the study, but were surveyed to determine pesticide exposure as a result of actual pesticide usages in the home and yard. Preliminary results indicated that a variety of pesticides were detected in house dust. The most prevalent were the older, persistent chlorinated hydrocarbons such as dieldrin, chlordane, and pentachlorophenol that were also frequently detected in NOPES (Lewis et al., 1994).[4]

Residential exposure to pesticides has been associated with a significant number of reported pesticide poisoning incidents involving children (Fenske et al., 1990; Berteau et al., 1989; Zweiner and Ginsburg, 1988). Zweiner and Ginsburg (1988) reported on organophosphate and carbamate poisonings among 37 infants and children in Texas. Fifteen percent of the children showed symptoms within 36 hours after their home had been sprayed or fogged with insecticide. One infant showed signs of organophosphate poisoning after sleeping on a treated carpet. Data collected from Poison Control Centers in 1992 indicated that nearly 63,000 exposures to pesticides (including disinfectants) had occurred in children under the age of 6 years (Litovitz and Holm, 1993).

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[4] It should be noted that most uses of dieldrin, chlordane, and pentachlorophenol have been canceled.

Fenske et al. (1990) measured chlorpyrifos concentrations in a carpeted apartment following treatment and found that the chlorpyrifos vapors measured in the infant's breathing zone (25 cm above the carpet) were significantly higher than in the sitting adult's breathing zone. It was suggested that although open windows provided dilution of air 1 m above the carpet, the treated carpet was a source of volatilized chlorpyrifos and concentrations near the floor were not as diluted (Fenske et al., 1990). Infants and toddlers may come into contact with these residues when crawling or playing on the floor.

LEGISLATIVE AUTHORITY

Legislative Basis

FIFRA provides a statutory framework under which EPA, primarily through a registration process, regulates the sale, distribution, use, and disposal of pesticides. As the standard for registration of a pesticide, FIFRA requires that the pesticide, when used in accordance with widespread and commonly recognized practices, will not cause unreasonable adverse effects on human health or the environment (7 U.S.C. section 136a(c)(5) and (7)). A similar standard applies to the reregistration of existing pesticide products and Agency approval of experimental use of unregistered pesticides (7 U.S.C. sections 136b(g)(2) and 136c). FIFRA defines "unreasonable adverse effects on the environment" as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of [the] pesticide" (7 U.S.C. section 136b(b)).

For the Agency to make well-informed "unreasonable adverse effects" determinations, FIFRA gives EPA broad authority, before and after registration, to require specific testing by registrants and/or applicants and submission of the resulting data to the Agency (7 U.S.C. sections 136 a, b, and c). Registrants and/or applicants are under a continuing obligation to provide the Agency with adequate information about their products to demonstrate that the products meet the statutory standard for registrability and to report any additional information that may affect the Agency's determination (7 U.S.C. sections 136a(c)(2)(B), 136b(b), and 136d(a)(2)).

Recently, the Food Quality Protection Act (FQPA) of 1996 was enacted. FQPA has amended FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA) to provide a comprehensive and protective regulatory scheme for pesticides. According to the U.S. EPA (1996), the new law mandates "a single, health-based standard for all pesticides in foods; provides special protections for infants and children; expedites approval of safer pesticides; creates incentives for the development and maintenance of effective crop protection tools for American farmers; and requires periodic re-evaluation of pesticide registrations and tolerances to ensure that the scientific data supporting pesticide registrations will remain up to date in the future." The law also has special provisions for minor use pesticides and antimicrobials, and will require that aggregate risks be evaluated.

EPA's Role in Providing Guidance

The Data Requirements for Registration (40 CFR 158) specify the types of data and information generally required to make sound regulatory judgements under FIFRA for each pesticide proposed for experimental use, registration, amended registration, or reregistration with respect to its potential for causing unreasonable adverse effects.

In 1983, guidelines were issued as a series of documents titled the "Pesticide Assessment Guidelines." The Guidelines describe acceptable protocols, test conditions, and the data that must be reported for each test requirement. The data requirements are intended to generate data and information pertaining to the identity, composition, potential adverse effects, and environmental fate of pesticides. The Guidelines were set forth as separate Subdivisions as follows:

- Subdivision D (Product Chemistry);
- Subdivision E (Wildlife and Aquatic Organisms);
- Subdivision F (Hazard Evaluation: Human and Domestic Animals);
- Subdivision G (Product Performance);
- Subdivision I (Experimental Use Permits);
- Subdivision J (Hazard Evaluation: Nontarget Plants);
    - Subdivision K (Reentry Exposure);
    - Subdivision L (Hazard Evaluation: Nontarget Insects);
    - Subdivision M (Biorational Pesticides (since revised under the title "Microbial and Biochemical Pest Control Agents");
    - Subdivision N (Chemistry: Environmental Fate);
    - Subdivision O (Residue Chemistry); and
    - Subdivision R Spray Drift.

Since 1987, a new Guideline document, Subdivision U: Applicator Exposure Monitoring, has been published. In addition, several position documents and addenda to the guidelines have been published.

Currently, the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) is harmonizing its pesticide and toxics guidance (i.e., the "Pesticide Assessment Guidelines") with similar international guidance such as that issued by OECD. The purpose of harmonizing these guidelines into a single set of OPPTS guidelines is to minimize variations among the testing procedures that must be performed to meet the data requirements of EPA under TSCA (15 U.S.C. 2601) and FIFRA (7 U.S.C. 136, *et seq.*). A goal of guideline harmonization is to reduce the data collection burden on industry as the results of a study conducted following harmonized guidelines may be used by a number of regulatory organizations/countries. In addition, harmonizing OPPTS Guidelines with those of the OECD will enable the Agency to achieve compliance with the OECD's Mutual Acceptance of Data Doctrine.

The harmonized OPPTS Test Guidelines are arranged into ten series as follows, each of which is broken down into a number of Groups:

- Series 810 - Product Performance Test Guidelines;
- Series 830 - Product Properties Test Guidelines;
- Series 835 - Fate, Transport, and Transformation Test Guidelines;
- Series 840 - Fate and Transport Field Studies Test Guidelines;
- Series 850 - Ecological Effects Test Guidelines;
- Series 860 - Residue Chemistry Test Guidelines;
- Series 870 - Health Effects Test Guidelines;
- **Series 875 - Occupational and Residential Exposure Test Guidelines**
    - Group A - Applicator Exposure Monitoring Test Guidelines (i.e., the existing Subdivision U Guidelines)
    - **Group B - Postapplication Exposure Monitoring Test Guidelines**;
- Series 880 - Biochemicals Test Guidelines; and
- Series 885 - Microbial Pesticide Test Guidelines.

The guidance being drafted in this document is Group B of Series 875 which includes a revision of the former Pesticide Assessment Guidelines - Subdivision K. Table A-1 depicts each of the Series 875, Group B Guidelines along with their former Subdivision K Guideline numbers (i.e., Series 130).

Please note that the QA/QC guidance in this document (i.e., Part C) should be used by investigators who are doing either Applicator Exposure Monitoring Studies or Postapplication Exposure Monitoring Studies.

REGULATIONS AND POLICIES

In conducting postapplication exposure monitoring studies, the study investigator needs to be cognizant of certain Agency regulations and policies that could impact investigation. For instance, research being conducted on human subjects must conform to the requirements of the "Common Rule." Further, investigations must be carried out following the requirements of the Good Laboratory Practices (GLPs) (40 CFR 160) and must comply with the requirements of the Worker Protection Standards (WPS) (40 CFR 156 and 170) and any labeled safety requirements, including those for products that are out of the scope of the WPS. Highlighted below are Agency regulations and policies that a study investigator must consider in pursuing postapplication exposure monitoring.

TABLE A-1. Postapplication Exposure Monitoring Guideline Numbers

GUIDELINE	SERIES 875 NUMBER	SUBDIVISION K NUMBER
Background and General Provisions	875.2000	130-1
Study Design	875.2000	Not included
Dislodgeable Foliar Residue Dissipation: Agricultural	875.2100	132-1
Transferable Residue Dissipation: Lawn and Turf	875.2100	Not included
Soil Residue Dissipation	875.2200	132-2
Indoor Surface Residue Dissipation	875.2300	Not included
Dermal Exposure	875.2400	133-3
Inhalation Exposure	875.2500	133-4
Biological Monitoring	875.2600	Not included
Product Use Information	875.2700	Not included
Descriptions of Human Activity	875.2800	133-1
Data Reporting and Calculations	875.2900	134

Protection of Human Subjects

Common Rule. The Federal Government has established common requirements for the protection of human subjects involved in research conducted or funded by a number of Federal Departments and Agencies including EPA and United States Department of Agriculture (USDA) (U.S. EPA, 1991). These requirements are known informally as "the common rule." EPA has adopted the common rule as regulations; they are codified at 40 CFR 26. The Agency is now drafting an order (EPA Order 1000.17 Human Subject Research) for implementing the policy set forth at 40 CFR 26.

FIFRA. In addition to the common rule, FIFRA also provides requirements for the protection of human subjects. Pursuant to FIFRA section 12(a)(2)(P), it shall be unlawful for any person "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test."

Worker Protection Standard. On August 21, 1992, EPA published the Worker Protection Standard Final Rule under the authority of FIFRA (U.S. EPA, 1992b). These regulations (codified at 40 CFR 156 and 170) were promulgated for the protection of workers from agricultural pesticides. The provisions of the Worker Protection Standard are directed toward the working conditions of two types of employees: those who handle agricultural pesticides (e.g., mix, load, apply, clean or repair equipment, act as flaggers, etc.) and those who perform tasks related to the cultivation and harvesting of plants on farms or in greenhouses, nurseries, or forests that may have been treated with pesticides (e.g., scouting, irrigation workers, and harvesters). The Worker Protection Standard includes provisions intended to: (1) eliminate or reduce exposure to pesticides; (2) mitigate exposures that occur; and (3) inform employees about the hazards of pesticides.

In conducting any field study, the investigator must ensure that the applicable provisions of the Worker Protection Standard regulations are being fulfilled. Generally, hazard information must be available for all workers, appropriate protective clothing must be provided, and decontamination sites and emergency assistance must be available. See Part C (QA/QC) for specific guidance on protecting human subjects involved in postapplication monitoring studies.

Good Laboratory Practices

The FIFRA Good Laboratory Practice (GLP) Standards are regulations that were promulgated to ensure the quality and integrity of data submitted to the Agency (U.S. EPA, 1989). "EPA originally published FIFRA GLP standards in the **Federal Register** of November 29, 1983 (48 FR 53946), which were codified at 40 CFR part 160....These regulations were promulgated in response to investigations by EPA and FDA during the mid-1970s that revealed that some [toxicological] studies had not been conducted in accordance with acceptable laboratory practices" (U.S. EPA, 1989). In 1989, EPA revised the GLPs to: (1) include the environmental testing provisions currently found in the TSCA GLP standards and; (2) apply to all data submitted to support registration/reregistration/special review of pesticides under FIFRA. "In summary, the FIFRA GLP standards will allow EPA to ensure the quality and integrity of all data submitted in support of pesticide product research or marketing permits" (U.S. EPA, 1989). Part C of this document (Quality Assurance/Quality Control) provides a detailed explanation of how to comply with the FIFRA GLPs.

GUIDELINE REQUIREMENTS -- AN OVERVIEW

EPA requires pesticide postapplication exposure data when it needs to determine: (1) a restricted-entry interval (i.e., the length of time required before persons could enter a pesticide-treated site without appreciable risk); or (2) if a pesticide could be used without appreciable risk in a residential setting. Generally, these data are required for highly toxic pesticides that have use types likely to result in significant dermal and inhalation exposure to persons entering treated fields or treated homes. The decision to require postapplication exposure data is made by examining the toxicity and exposure criteria detailed at 40 CFR 158.390.

At a minimum, dissipation, exposure, and toxicity data are needed to determine a restricted-entry interval and/or to assess risk. Dissipation may occur on foliage, soil, or indoor surfaces. The Agency may require one or more of the following studies to determine the dissipation rate, depending on the use of the pesticide: Dislodgeable or Transferable Foliar Residue (DFR) Dissipation Study; Soil Residue Dissipation (SRD) Study; or an Indoor Surface Residue (ISR) Dissipation Study. Guidelines for assessing dissipation are presented in Part B - Chapters 3, 4, 5, and 6. Exposure may occur via the dermal, inhalation, or nondietary ingestion routes. To determine human exposure, EPA may require Dermal Exposure (Part B - Chapter 7) or Inhalation Exposure (Part B - Chapter 8) studies. Nondietary ingestion exposure may be assessed using the guidance provided in Part B - Chapter 9. Alternatively, study investigators may choose to determine human exposure through Biological Monitoring (Part B - Chapter 10). Toxicity data are needed in conjunction with the dissipation and exposure data to estimate the restricted-entry interval or to ensure no appreciable risk from use in residential settings. No new toxicological studies are required under 40 CFR 158.390. Rather, the toxicological data needed are derived from studies required under 40 CFR 158.340. These data requirements are described in Subdivision F: Hazard Evaluation - Human and Domestic Animals. Finally, estimates may be refined by submitting dermal absorption data, product use information (Part B - Chapter 11), and descriptions of human activity (Part B - Chapter 12). Such information will allow the Agency to avoid using "worst-case" estimates. The types of studies that may be required are described in Table A-2. Selecting the types of studies required for estimating postapplication exposure is dependent upon the pesticide site and use patterns, potentially exposed populations, significant exposure routes, and the duration over which exposure occurs.

USE OF THE GUIDELINES

The information provided in this Background section is intended to provide the reader with an understanding of why postapplication data are required and how to determine which studies need to be performed. The next sections of this document -- Part B - Guidelines, Part C - QA/QC, and Part D - Exposure and Risk Assessment -- provide the actual "how-to" guidance on conducting and implementing postapplication exposure studies.

Each "Guideline" in Part B is labeled by an 875 number. This is in keeping with the OPPTS initiative to develop harmonized guidelines and numbering, as described earlier in this Background section. In addition to the Guideline of interest (e.g., Guideline 875.2500 - Inhalation Exposure), the

study investigator must at a minimum also consult Guideline 875.2000 - Background/Study Design, Part C - QA/QC, and Part D - Exposure and Risk Assessment/Calculations.

TABLE A-2. Description of Required Studies

Study	Description
Dissipation Studies	
Dislodgeable Foliar Residue (DFR) Dissipation Study (Agricultural) or Transferable Residue Dissipation Study (Lawn and Turf) Guideline 875.2100	DFR studies and transferable residue studies assess the dissipation rate of pesticides that can be dislodged and transferred from foliar surfaces (e.g., leaves of plants, turf, and garden plants) to human skin by analyzing foliar samples collected at various postapplication time intervals.
Soil Residue Dissipation (SRD) Study Guideline 875.2200	SRD studies assess the dissipation of pesticide residues in soil by extracting and measuring residues in soil collected at specified intervals postapplication.
Indoor Surface Residue (ISR) Dissipation Study Guideline 875.2300	ISR studies characterize dissipation of transferable pesticide residues from indoor surfaces as a function of time by sampling and analyzing surface residues at various time intervals following application.
Measurement of Human Exposure	
Dermal Exposure Guideline 875.2400	Passive dosimetry studies assess potential dermal exposure to humans by analyzing pesticide residues on dosimetry patches or clothing worn by study participants during reentry activities.
Inhalation Exposure Guideline 875.2500	Inhalation monitoring studies establish potential inhalation levels during postapplication activities by analyzing air samples collected via personal sampling pumps, passive monitors, high-volume samplers, or other techniques.
Nondietary Ingestion Exposure Assessment	Nondietary ingestion exposure may be estimated using residue data collected under one of the dissipation study guidelines above, and standard ingestion rates based on the age group or activity of interest.
Biological Monitoring Guideline 875.2600	Biological monitoring assesses internal dose by measuring either body burden or enzyme activity in selected tissues or fluid, or from the amount of pesticide or its metabolites eliminated from the body.
Other Data	
Product Use Information Guideline 875. 2700	The submission of product use information (e.g., typical use of the pesticide such as pounds applied) and its associated cultural practices allow more precise evaluation of exposure.
Descriptions of Human Activity Guideline 875.2800	Human activity data define the activity patterns that affect exposures. These data include site-specific and test subject-specific information.

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PART B

GUIDELINES

PART B - CHAPTER 1

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PART B - CHAPTER 1
BACKGROUND--GENERAL PROVISIONS
GUIDELINE 875.2000

1.1 PURPOSE AND SCOPE

These guidelines describe the postapplication monitoring data requirements (40 CFR 158.390) that may be required in support of registration.

1.2 DEFINITIONS

Terms used in Series 875, Group B have the meanings set forth at 40 CFR 152.3 and at 40 CFR 158. In addition, for the purposes of these guidelines key definitions are provided below:

Absorbed Dose. The amount of pesticide entering systemic circulation after crossing a specific absorption barrier (e.g., the exchange boundary of the skin, lung, or digestive tract); normally expressed as mass per unit body weight per unit time (e.g., mg/kg/day). Internal dose is a more general term denoting the amount absorbed with respect to specific absorption barriers or exchange boundaries (U.S. EPA, 1992).

Activity. A specific action related to a task or behavior that may result in an exposure event (e.g., harvesting pesticide treated crops, crawling on pesticide treated lawn) (also see Task).

Airborne Residue. Residues of a pesticide, including vapors and aerosols and other particulates that remain suspended in the air after pesticide application or that become suspended in the air at a treated site; normally expressed as a concentration, or mass per unit air volume (e.g., mg/m^3).

Ambient Reentry Concentration (ARC). The maximum level of pesticide residues at a treated site that is not likely to pose unreasonable adverse effects on people entering the site.

Analytical Method Development. The process by which scientific principles are applied to define the sample techniques that allow the reliable analysis of specific analytes of interest from a sample matrix.

Antimicrobial Pesticide. A pesticide that is intended to disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms; or protect inanimate objects, industrial processes or systems, surfaces, water, or other chemical substances from contamination, fouling, or deterioration caused by bacteria, viruses, fungi, protozoa, algae, or slime (FIFRA, Section 2).

Applied Dose. The amount of a substance presented to an absorption barrier (i.e., skin, lung, or digestive tract) and available for absorption, but not yet having crossed the outer boundary of an organism (U.S. EPA, 1992).

Average Daily Dose (ADD). Dose that is averaged over a specified time period taking into account the frequency, duration, and intensity of exposure during that time period. ADDs are usually expressed in units of mg/kg/day.

Control or Blank Samples. Sample media considered free of residues of any analyte(s) of interest that are handled, stored, shipped, and/or analyzed concurrently with a set or batch of exposure or residue samples. They are typically used to identify and quantify constant errors that affect a measurement. These samples are sometimes called blank samples.

Delivered Dose. The amount of a chemical available for interaction by any particular organ or cell (U.S. EPA, 1992).

Dermal Exposure. This term refers to a quantifiable measure of the amount of residue deposited on skin; normally expressed as a density, or mass per unit time, deposited on a defined skin surface area (e.g., mg/hr hand exposure); equivalent to potential dose for the dermal route.

Dislodgeable Residue. The amount of chemical residues deposited onto the leaf surface that have not been absorbed into the leaf or dissipated from the surface, and that can be dislodged by shaking leaf samples in a detergent solution ($\mu g/cm^2$).

Dissipation Curve. A graphical representation of pesticide residue levels plotted against time of sampling, or the mathematical representation of such a data.

Dose. A term referring generically to the amount of chemical to which an organism is exposed by any of several routes. Specifying the routes within the environmental context and especially the point of measurement is made possible via subcategories of dose (see Potential Dose, Applied Dose, Absorbed Dose, Internal Dose, and Delivered Dose). Dose is normally expressed as a mass per unit body weight per unit time and is frequently expressed in units of mg/kg/day.

Early Entry. The entry of people into a site previously treated with a pesticide prior to the expiration of any established, restricted-entry interval.

End-use Product. A pesticide product whose labeling: (1) includes directions for use of the product (as distributed or sold, or after combination by the user with other substances) for controlling pests or defoliating, desiccating, or regulating the growth of plants, and (2) does not state that the product may be used to manufacture or formulate other pesticide products (40 CFR 152.3).

Exposure. A measure of the environment leading to a dose. Exposure is quantified as the concentration of the agent in the medium in contact, integrated over the duration of the contact (U.S. EPA, 1992).

Exposure Monitoring Period. The length of time that the exposure-related activity of interest is monitored. For the purposes of these Guidelines, the duration over which each replicate is monitored should be representative of a typical activity (e.g., most occupational postapplication activities range from 4 to 8 hours) and be long enough to get quantifiable measurements. (See also Replicate and Work Cycle.)

Field Recovery. The data from experiments conducted to determine the loss of analyte from fortified sample collection devices in the field, when subjected to equivalent environmental conditions and exposure times as field exposure samples. Losses during shipping, storage, and laboratory operations, as well as field exposure to environmental factors (e.g., temperature, light), are included if the samples are handled and analyzed concurrently with the actual field samples.

Fortification. The process by which a known concentration of analyte is added to a sample matrix to assess loss during sample collection, transportation, or analysis.

Hazard Quotient. Unitless value that is calculated by dividing the average daily dose (mg/kg/day) by a value representing a toxicity endpoint (e.g., a reference dose; mg/kg/day).

Internal Dose. The amount of pesticide absorbed through the exchange boundaries of the body (equivalent to the absorbed dose).

Laboratory Recovery. Data from analyses conducted in the laboratory to determine the efficiency of recovery of the analyte from sample collection devices fortified at known levels. Laboratory recoveries reflect losses that occur during laboratory operations (e.g., extraction, cleanup, analytical measurements, etc.); they do not measure losses due to storage conditions or environmental factors. The purpose of laboratory recovery studies is to provide method development and validation data. Concurrent laboratory recovery samples need to be analyzed with the actual field samples to assess daily method performance.

Lifetime Average Daily Dose (LADD). Dose that is averaged over an individual's lifetime taking into account the frequency, duration, and intensity of exposure events. LADDs are usually expressed in units of mg/kg/day.

Limit of Detection (LOD). LOD is the point at which "a measured value becomes...larger than the uncertainty associated with it" (Taylor, 1987). The LOD can be defined in a number of ways, such as the background response plus three times the standard deviation of the lowest measurable concentration, three times the signal-to-noise ratio of baseline noise, three times the standard deviation of the lowest measurable concentration, etc.

Limit of Quantification (LOQ). LOQ is the point at which "measurements become quantitatively meaningful" (Taylor, 1987). It is the lowest pesticide residue that can be accurately quantitated in a reproducible fashion. The LOQ can be defined in a number of ways, such as the background response plus ten times the standard deviation of the lowest measurable concentration, ten times the signal-to-noise ratio of the baseline noise, ten times the standard deviation of the lowest measurable concentration, etc. In practice, the LOQ is the lowest fortification level that shows adequate recovery during the method validation process.

Margin of Exposure. Represents the ratio of a no observable adverse effect level (NOAEL) to an estimated dose/exposure level.

Method Validation. Process by which it is demonstrated that an analytical method is capable of measuring the magnitude of an analyte(s) of interest at a desired level of sensitivity and at acceptable levels of accuracy and precision for a specific matrix.

Percutaneous Absorption. The process by which pesticides pass through the skin barrier and enter systemic circulation; normally expressed as flux (mass per unit skin surface area per unit time), but may also be expressed as a percent (fraction of amount deposited on skin (exposure) reaching systemic circulation times 100) per unit time.

Personal Protective Equipment. Devices and apparel that are worn to protect the body from contact with pesticides or pesticide residues, including, but not limited to, coveralls, chemical-resistant suits, chemical-resistant gloves, chemical-resistant footwear, respiratory protection devices, chemical-resistant aprons, chemical-resistant headgear, and protective eyewear (40 CFR 170.240).

Pharmacokinetic Model. A model that can be used to predict the time course of absorption, distribution, metabolism, and excretion of a foreign substance in an organisms body (e.g., pesticide).

Potential Dose. The amount of chemical that could be inhaled without wearing a respirator, or which could be deposited on the skin without wearing clothing. Potential dose is typically expressed as a mass per unit body weight per unit time (i.e., mg/kg/day).

Proposed Restricted-entry Interval. A restricted-entry interval proposed by an applicant as adequate for human protection.

Quality Assurance. A "system of activities whose purpose is to provide to the producer or user of a product or service the assurance that it meets defined standards of quality. It consists of two separate but related activities, quality control and quality assessment." (Taylor, 1987).

Quality Control. The "overall system of activities whose purpose is to control the quality of a product or service so that it meets the need of users. The aim is to provide quality that is satisfactory, adequate, dependable, and economic." (Taylor, 1987).

Reentry. The entry of one or more people into a site subsequent to pesticide application.

Reentry Dose Level (RDL). Dose level at which reentry into an area previously treated with a chemical can occur with negligible deleterious effects caused by exposure to the chemical because the biological mode of action threshold for that chemical has not been met (mg/kg/day).

Replicate. An observation or set of observations relating to one exposure monitoring period for one test subject (or volunteer subject). For example, monitoring a reentry crew consisting of ten individual harvesters for one work cycle would involve ten replicates. For the purposes of these Guidelines, the duration over which each replicate is monitored should be representative of a typical activity (e.g., most occupational postapplication activities range from 4 to 8 hours) and be long enough to get quantifiable measurements.

Residue(s), Pesticide Residue(s), and Residue(s) of a Pesticide. Active ingredient(s), toxic impurities of the pesticide, toxic alteration products of the active ingredient, and/or manufacturing impurities of the pesticide that remain at the site of application or that remain on items that are subsequently removed from the site.

Restricted-entry Interval. The time after the end of a pesticide application during which entry into the treated area is restricted (40 CFR 170.3).

Sampling Interval. The day or hour postapplication which samples for a given study are collected (e.g., 4 hours, 1 day, 2 days, etc.).

Sampling Period. The length of time over which samples are collected at various sampling intervals to characterize dissipation.

Site. A site refers to any plant, animal, object or location to which a pesticide is applied or which is protected by an adjacent application of a pesticide. Examples of sites are: crops, ornamental plants, lawns, stored commodities, domestic animals, households, wood structures, aquatic areas, boats, food processing plants, hospitals, plastic products, humans, and garbage dumps.

Storage Stability Study. A storage stability study determines the stability of analyte(s) in or on appropriate substrates under similar storage conditions that will be used to store field samples. Fortified sampling devices must be stored for the maximum amount of time and under the conditions expected to be encountered for field samples. Storage stability includes losses during storage and laboratory operations. A storage stability study can be conducted prior to or in conjunction with a field study.

Surrogate, Surrogate of a Pesticide, or Pesticide Surrogate. A chemical compound or a mixture of compounds other than the pesticide being investigated that could be used to quantify human exposure to the pesticide being investigated. The surrogate could be an active ingredient of a pesticide registered for that use or a very similar use.

Task. A human work activity performed according to current commonly-recognized practice, or any other human activity that could result in exposure to pesticide residues at the site (also see Activity).

Transfer Coefficient. An estimate of the rate of residue transfer to humans that occurs from a pesticide-treated surface during the performance of specific work or other activity, generally expressed in units of cm^2/hour. For example, in agricultural settings, transfer coefficients are calculated as the ratio of worker dose (ug/hr) to dislodgeable residue (ug/cm^2).

Transferable Residues. That portion of applied pesticide residues that area available for nondietary transfer to humans. May be measured by several techniques that do not involve the quantification of total residues in the matrix that is treated.

Travel Recovery Samples. Travel recovery samples account for the stability of the analyte on each sampling matrix during shipment. Travel recovery samples provide useful information for determining whether the analyte losses occurred during sample shipment. Travel recoveries do not account for losses due to environmental conditions during sampling in the field.

Typical End-use Product. A pesticide product that is representative of a major formulation category (e.g., emulsifiable concentrate, granular).

Use Type. A grouping of crops, plants, or situations with similar potential for exposure during postapplication activities.

Watering-in. Irrigation following pesticide application to lawns or turf. For some pesticides, this practice is recommended to move product from blades to thatch and soil.

Work Cycle. A definable sequence of tasks that may be repeated any number of times within one day or less (e.g., for ornamentals, one work cycle could be cutting, bundling, and grading of chrysanthemums). An exposure monitoring period should span at least one, but may include multiple work cycles (see also Exposure Monitoring Period and Replicate).

1.3 REQUIREMENT FOR POSTAPPLICATION EXPOSURE AND SUPPORTING DATA

A restricted-entry interval is required under the provisions at 40 CFR 158.520 (formerly 40 CFR 158.390) to support the registration of each end-use product that meets one or more of the toxicity criteria specified below, and that has a use type that could be included in the use classifications specified below. Postapplication data are also needed to determine if a pesticide can be used in a residential or commercial setting without appreciable risk to humans.

1.3.1 Toxicity and Exposure Criteria

As delineated at 40 CFR 158.520, postapplication exposure data may be required when at least one of the toxicity criteria and one of the exposure criteria are met, as follows:

Toxicity Criteria

- The acute dermal LD_{50} of the technical grade of the active ingredient (TGAI) is less than 2000 mg/kg (i.e., Toxicity Categories I and II);
- The acute inhalation LC_{50} of the TGAI is less than 0.5 mg/L (4 hour study);
- The acute oral LD_{50} of the TGAI is less than 50 mg/kg (i.e., toxicity category I);
- Other adverse effects have been observed in any of the following toxicity studies: carcinogenicity (Guideline 83-2), neurotoxicity (Guideline 82-6, 82-7), reproduction (Guideline 83-4), and chronic feeding (including immunotoxicity testing) (Guideline 83-1); developmental toxicity (Guideline 83-3, 83-6); or

- Epidemiological/poisoning incident data indicate that adverse effects result from postapplication exposure.

Exposure Criteria

- Pesticide will be applied to crops or in areas related to agricultural commodity production where human tasks will involve postapplication exposure to pesticide residues; or
- Pesticide will be applied to nonagricultural outdoor sites such as home lawns where human exposure may occur; or
- Pesticide will be applied to indoor sites, either residential, commercial, industrial, or agricultural, where human postapplication exposure may occur.

The toxicity and exposure criteria are currently being developed by the Agency for antimicrobials and will be added to these Guidelines at a later date.

1.3.2 Waivers

General waiver. An applicant for registration may request a waiver from the requirement to submit some or all of the data required by 40 CFR 158.390 and described in Series 875, Group B provided that written evidence is submitted that such data are inapplicable to the specific pesticide or product. Detailed information on requesting waivers may be found at 40 CFR 158.45.

Waiver for no substantial exposure. The applicant may provide a description of sites and human reentry activities revealing that no substantial human exposure to pesticide residues can be reasonably foreseen. If the applicant also requests a waiver from the requirement to provide a restricted-entry interval on a particular product label, the Agency will review the request and the descriptions submitted. If the Agency agrees with the submitted rationale, it will grant a waiver.

Waiver for other specific reasons. The applicant may request a waiver from submittal of certain data required by 40 CFR 158.390 and discussed in Series 875, Group B, if evidence is submitted that specific properties or characteristics of the pesticide or product preclude the requirement for such data. Such properties or characteristics could include, but are not limited to, the composition, degradation rate, toxicity, and such other chemical and physical properties of a specific pesticide or product that are fundamentally different from the factors considered by the Agency in the establishment of the data requirements of 40 CFR 158.390.

1.3.3 Formulators' Exemption

As provided by 40 CFR 158.50, an applicant for registration of an end-use product who purchases and legally uses a registered product to formulate the end-use product is not usually required to submit or cite data discussed in Series 875 - Group B. Such a purchased product must be registered and labeled for manufacturing use or for the same use as the end-use product being formulated by the applicant. This is consistent with the Congressional intent as set forth in sec. 3(c)(2)(D) of FIFRA, which provides that:

> "No applicant for registration of a pesticide who proposes to purchase a registered pesticide from another producer in order to formulate such purchased pesticide into the pesticide that is the subject of the application shall be required to: (i) submit or cite data pertaining to such purchased product; or (ii) offer to pay reasonable compensation otherwise required by [3(c)(1)(D) of FIFRA] for the use of any such data."

Because studies required by 40 CFR 158.390 and discussed in these guidelines would ordinarily be conducted by the basic manufacturer, pesticide formulators would not often be expected to conduct such tests themselves to develop data to support their individual products. They may do so if they wish, but they usually rely on data developed by the manufacturing use producer, unless the basic manufacturer no longer supports the registered use. Then, the data burden is on the formulators.

1.4 GENERAL REPORTING REQUIREMENTS

In brief, reporting of study results must follow the provisions described in PR 86-5 and under the Good Laboratory Practices (GLP) at 40 CFR 160.185. Generally, the GLP provisions provide information on the format of submitted studies. Other formatting requirements are listed under the Data Requirements for Registration at 40 CFR 158.32. Units of measurement should be in the metric system.

1.5 COORDINATION WITH OTHER REQUIREMENTS IN 40 CFR PART 158

The applicant should determine whether studies conducted to meet the requirements of 40 CFR 158.390 can be coordinated with studies required by other sections of 40 CFR 158, such as 158.640 discussed in Subdivision G (Product Performance); 158.540 discussed in Subdivision J (Hazard Evaluation: Nontarget Target Plants); 158.290 discussed in Subdivision N (Chemistry Requirements: Environmental Fate), and 158.240 discussed in Subdivision O (Chemistry Requirements: Residue Chemistry). The studies should be coordinated with the data gathered to meet the requirements of 40 CFR 158.340 discussed in Subdivision F (Hazard Evaluation: Humans and Domestic Animals) and with information from Subdivision I (Experimental Use Permits). The applicant should also be cognizant of the labeling implications of this Series in relation to Subdivision H (Label Development).

1.6 TOXICITY DATA REQUIRED

The toxicological data submitted by registration applicants to evaluate the toxicity of a pesticide to humans and domestic animals, as required by 40 CFR 158.340, should be used to determine a restricted-entry interval or evaluate any risks associated with postapplication exposure scenarios. Those data are described in the following sections of Subdivision F. Detailed information on using those data to determine the restricted entry interval is provided in Part D, Chapter 2 - Calculations.

Sections of Subdivision F

Acute Testing		
Acute oral toxicity - rat	81-1	870.1100
Acute dermal toxicity	81-2	870.1200
Acute inhalation toxicity - rat	81-3	870.1300
Primary eye irritation - rabbit	81-4	870.2400
Primary dermal irritation	81-5	870.2500
Dermal sensitization	81-6	870.2600
Delayed neurotoxicity (acute) - hen	81-7	870.6100
Acute neurotoxicity - rat	81-8	870.6200
Subchronic Testing		
90-Day oral - two species, rodent and nonrodent	82-1	870.3100 870.3150
21-Day dermal	82-2	870.3200
90-Day dermal	82-3	870.3250
90-Day inhalation - rat	82-4	870.3465
28-Day delayed neurotoxicity - hen	82-6	870.6100
90-Day neurotoxicity - rat	82-7	870.6200
Chronic Testing		
Chronic feeding - two species, rodent and nonrodent	83-1	870.4100
Carcinogenicity - two species, rat and mouse preferred	83-2	870.4200
Developmental Toxicity and Reproduction		
Developmental toxicity - two species, rat and rabbit preferred	83-3	870.3700
Reproduction	83-4	870.3800
Postnatal developmental toxicity	83-6	870.6300
Mutagenicity Testing		
Salmonella typhimurium reverse mutation assay	84-2	870.5265
Mammalian cells in culture	84-2	870.5300
In vivo cytogenetics	84-2	870.5380 870.5385 870.5395
Special Testing		
General metabolism	85-1	870.7485
Domestic animal safety	85-2	870.7500
Dermal penetration	85-3	870.7600
Schedule controlled operant behavior	85-5	870.7800
Peripheral nerve function	85-6	870.6850
Immunotoxicity	85-7	870.7800

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PART B - CHAPTER 2

STUDY DESIGN

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PART B - CHAPTER 2
STUDY DESIGN
GUIDELINE 875.2000

2.1 INTRODUCTION

The Agency requires that, when certain toxicity and exposure criteria have been triggered (as delineated at 40 CFR 158.390), postapplication monitoring data be submitted. These data may include human exposure and chemical dissipation data (e.g., dislodgeable foliar and transferable residues). The first step in undertaking any postapplication monitoring study is to develop a study design. The Agency requires investigators to submit draft study protocols for review prior to initiating work on a study. Along with the other components of the study design described in this Guideline, these draft protocols should include contingency plans for major weather events, attrition of study participants, or other circumstances that may adversely affect successful completion of the study. All protocols must also be developed in accordance with the requirements stipulated in 40 CFR 160: *FIFRA Good Laboratory Practices* (U.S. EPA, 1989). They should also provide a comprehensive rationale for the choice of sites and activities to be monitored as well as other aspects of the study (e.g., crop selection, season of activity). Agency review of draft protocols is **required** to provide registrants with clarification concerning the scope of each study. Additionally, protocol review by the Agency prevents misinterpretation of the study during regulatory action based on the data generated in the study.

This Guideline provides an overview of the key study design considerations required to conduct studies under Series 875, Group B. Section 2.2 - Experimental Design addresses factors such as the selection of sites and activities to monitor, and issues associated with geographic and seasonal variability. Section 2.3 - Number of Samples and Replicates addresses the numbers of human exposure and environmental data points required for study completion. Section 2.4 - Test Safety describes the requirements for protecting human test subjects involved in research activities. Section 2.5 - Materials and Methods includes information concerning selection of the test material, pesticide application processes, and monitoring techniques for determining both human exposure and environmental concentrations. Section 2.6 - Sample Handling and Collection Procedures addresses general requirements associated with handling and collecting samples and Section 2.7 - Analytical Chemistry provides general guidance on the types of information that should be included in the study design protocol on the analytical chemistry methods used. Study design requirements for ensuring the quality and reliability of the data are described in Section 2.8 - Quality Assurance and Quality Control. This guideline also describes critical elements of Good Laboratory Practices (40 CFR 160) that should be considered during the study design phase. Additionally, contingency planning and reporting and record keeping issues are described in Sections 2.2 and 2.10. The discussion in this Guideline is limited to the design of studies aimed at gathering postapplication exposure and chemical dissipation data. Sampling techniques, monitoring methods, and other data requirements are described in Part B, Chapters 3 through 12. Details on fulfilling quality assurance and quality control needs are described in Part C. The toxicity data used in the calculations are from data generated under 40 CFR 158.340 requirements. Guidance for calculations based on the resulting data are provided in Part D.

2.2 SITE SELECTION CONSIDERATIONS

The first step on designing a postapplication exposure monitoring or chemical dissipation study is to consider the following five questions:

- Which use patterns and activities should be monitored?
- Which geographical and climatological regions should be monitored?
- What sites should be monitored?
- In what seasons should monitoring occur?
- What use patterns reflect critical market share?

Generally, investigators should choose a combination of sites, activities, and geographical/climatological regions that represent the use of a pesticide product and that will be reflective of the toxicological endpoint of concern. For example, for a compound with a dermal toxicity endpoint, postapplication monitoring should be conducted for activities that could result in dermal exposure. Agency assessments are based on endpoints specified in *Toxicology Endpoint Selection Documents* by the Health Effects Division of the Office of Pesticide Products under *Subdivision F: Toxicology, Human and Domestic Animals* (40 CFR 158). Investigators are required to submit protocols prior to the initiation of any study in order to provide the Agency with a chance to review the design and to provide comments to ensure that the data generated will be appropriate to address the questions concerning the safety of the pesticide product in question.

Pesticide active ingredients may be registered to control a wide variety of target pests in agricultural, industrial/commercial, and residential settings (e.g., a household insecticide may also be registered to control leaf miners in tomatoes and as a fly control agent in a food processing facility). When designing a study, investigators must decide which uses should be monitored and which uses can be considered representative of several pesticide product uses in the risk assessment process. This is necessary because, for many chemicals, it is not feasible to generate data for every possible exposure scenario. The Agency recommends that such decisions be made based on a strategy that considers application rates and frequency, potential for exposure, geographic and climatic regions, and market share. Investigators are encouraged to utilize the guidance provided in Figure B2-1 and in Sections 2.2.1 through 2.2.5 in the site selection phase. A decision logic is presented in Figure B2-1 that addresses each of these critical issues. This guidance may also be used to assist investigators with the development of an overall strategy for completing studies in support of their products. Chester (1993) and Fenske and Teschke (1995) also provide guidance pertaining to the design and conduct of pesticide exposure studies.

2.2.1 Use Patterns and Activities

During agricultural reentry, a worker may perform various tasks such as thinning, crop harvesting, and canopy management. Commercial/industrial reentry activities can include work with treated oil drilling muds, entry into fumigated shipping containers, and contact with sanitized surfaces in a health care facility. Residential reentry activities of concern include children playing on treated lawns, inhalation exposure resulting from a termiticide application, and nondietary ingestion of chemical residues due to mouthing an object contaminated with pesticide residues. In the study design, investigators need to specify which activities will be monitored during the study (e.g., pruning, picking, playing, etc.). Investigators should also provide justification for why those activities were selected.

The following factors should be considered in deciding which activities/use patterns to monitor:

- Magnitude of Exposure. For some long-term effects (i.e., carcinogenicity), the study investigator may decide to monitor activities that would result in typical exposure (i.e., provide data on the central tendency). Conversely, for short-term acute effects the investigator may monitor activities that would result in worst-case exposures (i.e., high-end) . Investigators should not select sites that will minimize the potential for exposure based on some obvious factor such as mechanical vs. hand harvesting of the same crop.

- Representativeness. The chosen activity should be representative. Representativeness should be based on whether the monitored activities are reflective of the activity of interest or whether the use pattern is typical for the pesticide product. For example, in indoor scenarios such as residential exposure after a termiticide treatment, investigators should consider construction type and ventilation patterns. Data generated from a house with a basement in Maryland may not serve as an adequate surrogate for a typical slab house in Florida because of construction type and the regional use pattern. In addition, sampling should be done in the zone of contact to ensure that sample results are representative of human exposures. For example, sampling should occur in those parts of the crop where workers conduct their activities (i.e., it may not be necessary to sample on the border of a crop where there is little contact). Investigators must also be careful not to alter typical behavior patterns of test subjects during any study (e.g., sampling techniques must be as unobtrusive as possible). If the monitoring technique, regardless of which is selected, interferes with the behavior of the test subject,

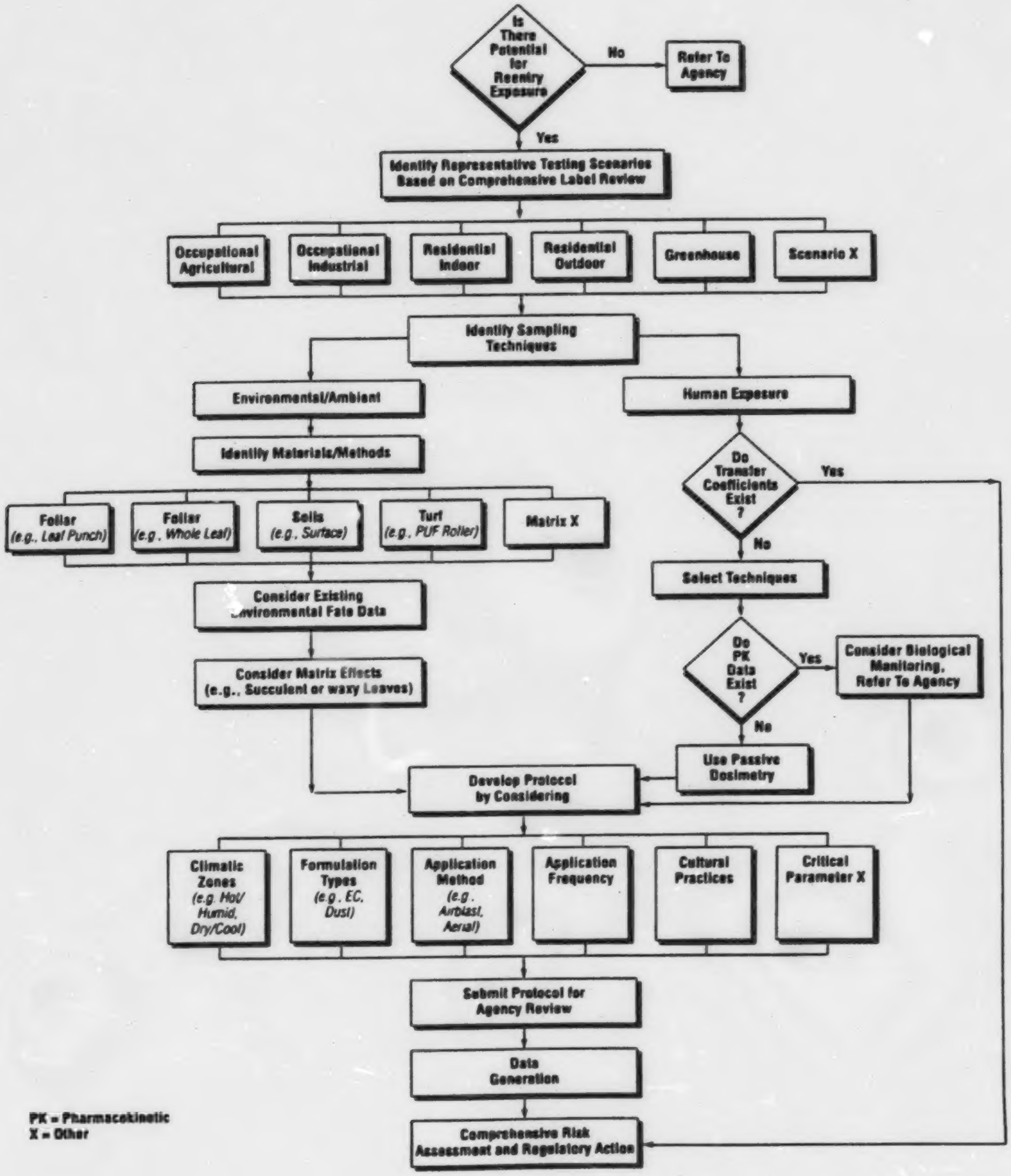
Is There Potential for Reentry Exposure
No
Refer To Agency
Yes
Identify Representative Testing Scenarios Based on Comprehensive Label Review
Occupational Agricultural
Occupational Industrial
Residential Indoor
Residential Outdoor
Greenhouse
Scenario X
Identify Sampling Techniques
Environmental/Ambient
Human Exposure
Identify Materials/Methods
Foliar (e.g., Leaf Punch)
Foliar (e.g., Whole Leaf)
Soils (e.g., Surface)
Turf (e.g., PUF Roller)
Matrix X
Consider Existing Environmental Fate Data
Consider Matrix Effects (e.g., Succulent or waxy Leaves)
Do Transfer Coefficients Exist ?
Yes
No
Select Techniques
Do PK Data Exist ?
Yes
Consider Biological Monitoring, Refer To Agency
No
Use Passive Dosimetry
Develop Protocol by Considering
Climatic Zones (e.g. Hot/ Humid, Dry/Cool)
Formulation Types (e.g., EC, Dust)
Application Method (e.g. Airblast, Aerial)
Application Frequency
Cultural Practices
Critical Parameter X
Submit Protocol for Agency Review
Data Generation
Comprehensive Risk Assessment and Regulatory Action
PK = Pharmacokinetic
X = Other

Figure B2-1. Decision Tree for Site/Activity Selection

investigators must describe the effects and how the monitored exposure levels may be impacted.

- Cultural and Use Practices. Cultural practices can vary within regions for particular sites. As a result, variability in cultural practices should be considered. For example, orchard fruit harvesting may be completed using ladders and baskets or with mobile power equipment (i.e., cherry pickers). Additionally, practices may vary in commercial/industrial uses. For example, varying types of ventilation practices exist in facilities where antimicrobial pesticides are added to industrial processes and products.

2.2.2 Geographic and Climatological Considerations

A monitoring study must take place in a location and climate similar to that of the use pattern of interest. Factors to consider in identifying geographical and climatic regions for outdoor monitoring studies (e.g., agricultural reentry or lawn/turf residential exposure) include the following:

- Representativeness. Data must be collected in those geographic regions where the chemical is used (e.g., almonds are grown almost exclusively in California). The Agency has developed a map that delineates regions for completing studies under *Subdivision O: Residue Chemistry*. The map divides the United States into 13 distinct regions. (See Figure B2-2.) Investigators should consider these regions when defining the types and numbers of studies that are to be completed in support of a pesticide active ingredient (i.e., the defined regions may assist investigators in defining chemical use regions).

- Climate. The study must be conducted in a climate that is typical for the pattern of interest. Investigators are encouraged to consult National Weather Service data to determine if climatic differences exist between regions for the pesticide of interest. Contingency plans for catastrophic or atypical weather events must also be considered in the design of the study (e.g., fluke rainstorm in arid California region during a foliar dislodgeable residue study). Refer to Part C, QA/QC -- for detailed information on acceptability criteria for providing climatological data.

- Miscellaneous. Several environmental factors, such as soil types, cultural practices, and pest populations, may vary among regions. Significant variations among cultural practices can occur as a result of these factors. Study investigators should consider regional practices and label requirements when developing study designs.

In the study design, the source and type of weather data to be collected must be specified. Minimally, data on air temperature, humidity, and rainfall during the monitoring period must be collected. Other data such as wind speed/direction and soil temperature should also be considered as

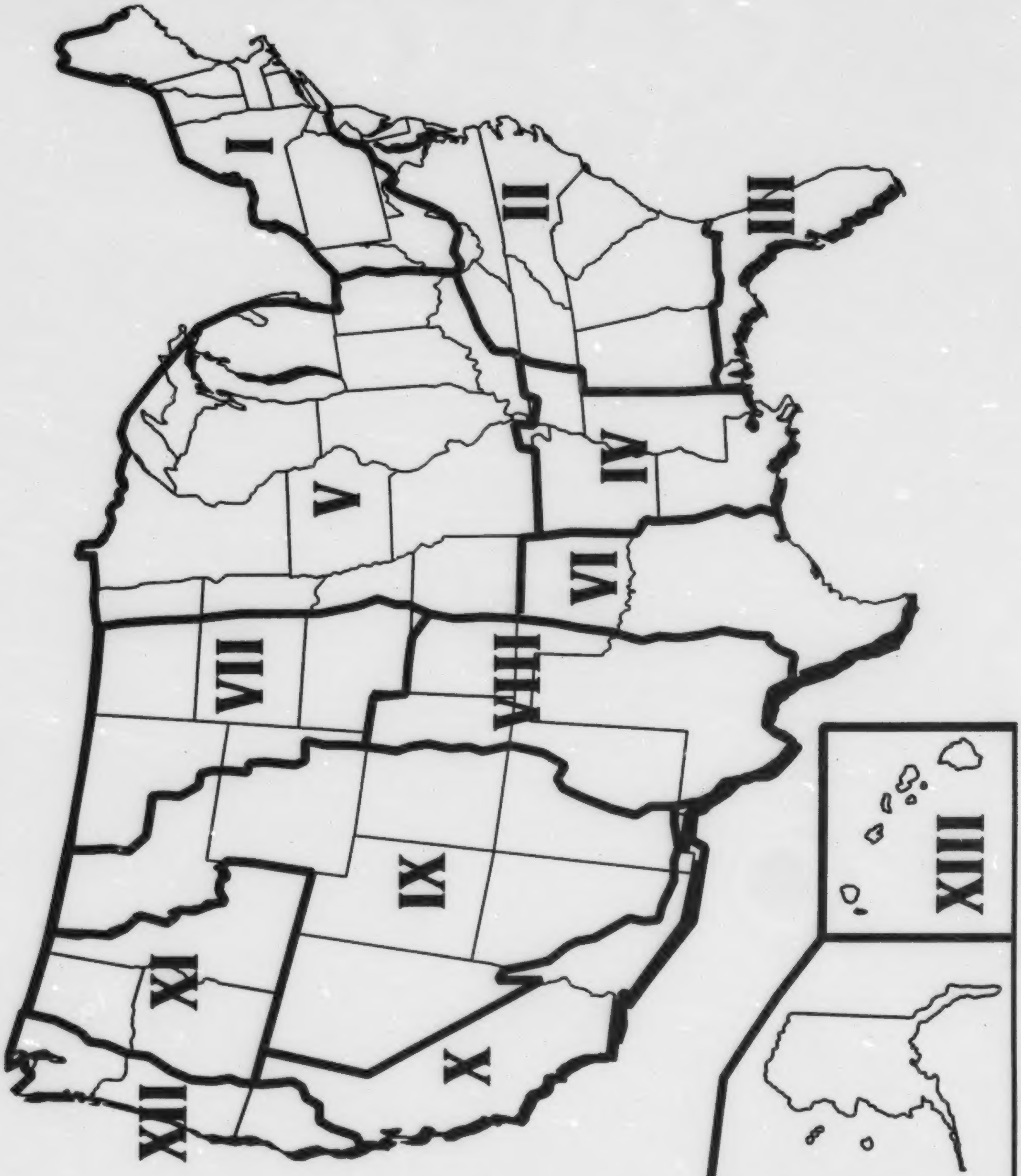
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII

Figure B2-2. Residue Chemistry Trial National Regions

appropriate. Surrogate data from a nearby site may be acceptable, but discretion in the use of such data is advised. On-site monitoring of rainfall is highly recommended.

For indoor sites, the following should also be considered:

- Geographic Variation. Use patterns, construction techniques, and other factors that may affect indoor postapplication exposure to pesticides on a regional basis must be considered. Termiticide use in the Northeast versus Florida is an appropriate example. Generally, construction types vary within regions. Basements are not common in Florida due to the water table, but they are common in the Northeast. Termiticide application techniques vary due to construction types. Varying techniques may impact inhalation exposure levels.

- Climatic Variation. Indoor monitoring may be impacted by climatic variation as these variations may affect both construction types and human behavior patterns. Generally, residences are less insulated in warmer climates. Hence, air exchange rates for those types of buildings are generally higher (i.e., more dilution of indoor air contaminants is likely). Additionally, air conditioning (HVAC) systems may be used more frequently in warmer climates.

2.2.3 Sites/Populations to Monitor Within a Region

Once investigators have identified which activities/use patterns and geographic/climatic regions are appropriate, a specific site/population must be identified within a selected region for monitoring purposes. Generally, these sites must represent a "worst case" potential for exposure unless investigators can otherwise justify the use of a different scenario.

In choosing outdoor sites, the investigator must consider four factors:

- Crop Canopy/Maturity. For candidate agricultural sites within a geographic/climatic region, investigators should consider the level of the crop canopy and general maturity of the crop as it relates to typical reentry activities. This is critical as it is believed that dermal exposure levels may be directly related to the extent of contact with foliage and the maturity of the foliage (i.e., dermal exposure during agricultural reentry is generally the predominant exposure route). Investigators should be careful to select residential sites that are typical of the turf in the region (e.g., common grass variety, numbers of pesticide applications, fertilizers, etc.).

- Cultural Practices. For candidate sites within a geographic region, investigators should consider cultural practices. Cultural practices may include grape canopy management, tree trimming/propping, turf mowing, and grape girdling. The impact of variations in cultural practices within regions is difficult to quantify. However, it is likely that such variability can impact exposure levels for a given reentry activity (e.g., grape trellising and girdling practices between growers in California may vary enough to impact exposure levels within the region).

- Populations. Within geographic regions there are often occupational populations that complete various reentry activities. Investigators should consider the levels of experience within a subject population in the design of the study. The individuals chosen for the study should be representative of the exposed population. Ideally, the test population should be involved in the type of work on a regular basis and be familiar with the activities and purpose of the study. For example, test subjects should be normal workers and not inexperienced volunteers. Likewise, for residential studies, the test populations should be representative of the exposed homeowners/residents population.

- Representativeness. Within a region, representativeness depends upon the crop canopy, the associated cultural practices, and the populations who are subject to human exposure monitoring. Investigators should be careful to assess each of these issues within a region that has been selected for a study. Investigators should provide in any submission to the Agency a rationale detailing the general and specific aspects of the site selection process.

When choosing indoor sites, investigators must consider two additional factors:

- Construction Type. Pesticides can be applied in residential, commercial, and industrial indoor settings. Construction type may impact the distribution and longevity of chemical residues within treated buildings because of the differences in air exchange rates, insulation levels, hard surface types, and the general use of common construction materials. Investigators should consider these parameters in the study design process. For example, if postapplication inhalation exposure after a termiticide application is to be monitored, investigators should address the four basic residential construction types (i.e., slab, basement, crawl space, and plenum) in their protocols.

- Ventilation Procedures. One of the key concerns for the Agency is addressing postapplication inhalation exposure after indoor treatments of a pesticide. Along with construction type, the air exchange rate is probably the most critical parameter that affects airborne concentrations over time. Therefore, air exchange rates must be considered by investigators in the design of their studies. Generally, investigators should describe the use of any ventilation (i.e., HVAC and/or natural) over the course of a study and should describe the dimensions/layout of any building under study.

2.2.4 Time of the Year for Monitoring

Studies should be conducted during the season(s) when exposure is of most concern and where conditions pose the greatest risk for human exposure. For any postapplication monitoring, data must be collected during the season that the particular exposure scenario normally occurs (e.g., agricultural reentry during a typical harvest season, indoor residential air during common pest seasons, etc.).

2.2.5 Market Share

In developing a strategy to support labeling for an active ingredient, investigators should consider all uses that are allowable by current or proposed labeling as well as the core market for their product. Market share analysis can assist investigators in the development of a strategic plan for selecting and designing their studies (e.g., typical and unusual application rates, seasons, crops, etc.). Investigators should consider the possible confidential nature of this type of information if they are to be included in a study protocol.

2.3 NUMBER OF SAMPLES AND REPLICATES

The numbers of datapoints generally required under Series 875, Group B are presented below for human exposure monitoring and the characterization of chemical dissipation in the environment as well as in residential, commercial, and industrial settings. Both the number of sites required for each type of monitoring and the number of replicate datapoints at each site are described. The number of samples and replicates presented below are general guidance. Investigators are required to submit protocols prior to initiating any study to ensure that an adequate dataset is generated.

Chemical Dissipation. A dissipation study involves taking a number of samples over a period of time to characterize the rate of dissipation of a pesticide. Such a study would start on the day of pesticide application. (See Part B, Chapters 3, 4, 5, and 6 for further description of the sample collection methods.)

- Geographic Location. The study investigator should carry-out dissipation studies at a number of locations. Generally, samples are collected at a minimum of three sites. Sampling at multiple sites is usually necessary to ensure that the varying climatic conditions, crops, and pest types are represented. The location and number of sites selected for use in a study must be justified by investigators to the Agency. Investigators will need to justify site selection based on the criteria described above (e.g., on the nature of the use scenario and the number of regions where the target crop is grown or structural pests are located).

- Sampling Period and Intervals. The dissipation study should be carried out over a long enough period to characterize the dissipation rate of the pesticide under investigation. Generally, the first sampling intervals will be just before and after application (i.e., t=0). Subsequent samples should be collected (that are appropriate for the pesticide under investigation) at periodic intervals over the course of the study. During each sampling interval, a minimum of 3 replicate samples need to be collected at each treated study site.

Human Exposure Study. A human exposure study involves determining the amount of pesticide exposure that occurs during a given activity. (See Part B, Chapters 7, 8, and 10 for further description of these requirements.)

- Number of Subjects to Monitor. Generally, a minimum of 15 monitoring replicates need to be completed for each reentry activity of concern. Investigators should attempt to obtain data from as many test subjects as inter-test subject differences are a primary source of variability. The statistical robustness of the data set will increase with increased number of replicates.

- When to Monitor. Generally, exposure replicates should be completed based on the following distribution: 5 replicates/day on each of 3 days after the application of the pesticide product. Monitoring should be conducted before residues have dissipated beyond the limit of quantification.

2.4 TEST SAFETY

In the study design, it should be indicated what clothing will be worn by the subjects in the study. For example, will normal work clothes be worn, and will any form of personal protective equipment be used? The type of personal protective equipment recommended for the pesticide of interest should be considered during the study design phase. Regulations that must be considered in making the decisions about protection of study participants include those of the country where the study is being conducted. For example, in the United States, these regulations include the Worker Protection Standard and Informed Consent. These are described below.

The Worker Protection Standard. In conducting any field study, the investigator must insure that the applicable provisions of the Worker Protection Standard regulations are being fulfilled. Generally, hazard information must be available for all workers, appropriate protective clothing must be provided, and decontamination sites and emergency assistance must be available. To determine what you must do to comply with the Worker Protection Standards, refer to the Code of Federal Regulations (40 CFR Part 170) and/or contact the Certification and Worker Protection Branch, Office of Pesticide Programs, U.S. EPA at (703) 305-7666.

Informed Consent. Investigations carried out under these guidelines must be properly designed to provide for maximum protection of the study subject's health. Studies conducted to obtain human exposure data must not violate Section 12(a)2(P) of FIFRA. Specifically, informed consent should be obtained in writing from all subjects who will be exposed as a result of these studies. Also, proposed protocols may need to be approved by the appropriate human studies committee for the state in which the exposure will occur. Investigators are also encouraged to review the requirements of the *Federal Policy for the Protection of Human Subjects; Notices and Rules* otherwise referred to as the "Common Rule" (U.S. EPA, 1991).

2.5 MATERIALS AND METHODS

This section includes a general description of the study design considerations for selecting an end-use-product test material, defining an application method, and developing a monitoring strategy. Selection of a proper test material is dependent upon the labeling for each end-use-product, and the physical-chemical properties of the pesticide active ingredient in the product. Selection of a proper application method should be reflective of the exposure scenario to be monitored. Additionally, techniques used to monitor human exposure and environmental dissipation should be durable and provide appropriate data (e.g., biological monitoring would not be used for a chemical with no pharmacokinetic data). Monitoring techniques are described in Part B, Chapters 3 through 8 and in Chapter 10 of this document. Refer to these chapters for specific information regarding the technology and methods recommended by the Agency for developing field monitoring data. The Agency encourages the use of novel or alternative technologies for generating data to satisfy these guidelines. However, if investigators opt to develop data using such an approach, a justification for the approach must be prepared and submitted to the Agency as part of the study protocol for review purposes prior to the initiation of any such study.

2.5.1 Test Material

Typically, active ingredients are marketed in several formulations. As such, investigators must select which formulations will be used as test materials in any study to support their product. Representative end-use product formulations (e.g., wettable powder, emulsifiable concentrate) must be used to make all treatment(s) to the site under investigation. Significant differences in residue dissipation rates and exposure levels are thought to exist among different end-use products containing the same active ingredient (e.g., the wettable powder formulation of a given pesticide may be more persistent than the emulsifiable concentrate). Therefore, the end-use product to be applied must be the formulation type that is most likely to be persistent and/or that inherently poses the highest risk in terms of exposure during reentry operations. The study design must include a description of the formulation to be used in the study, and a rationale for selecting the formulation.

2.5.2 Pesticide Application

The method of application (groundboom spray, airblast spray, broadcast granular, etc.) should be specified, and the type of equipment to be used should be indicated. Generally, the pesticide should be applied so that the greatest exposure potential is achieved (i.e., highest allowable rates with minimum intervals between applications). However, if the pesticide under consideration is known to be a carcinogen, then typical application rates may be more appropriate. The pesticide must be applied under conditions that are consistent with the label requirements of the formulated end-use product.

2.5.3 Description of Methods For Monitoring Pesticide Concentration

The study design should provide a description of which methods will be used to measure each of the analytes under investigation (e.g., PUF roller, hand washes for dermal, etc.) in each of the matrices (e.g., air, soil, foliar) of concern. For inhalation exposure, the technique (pump/absorbers, impingers, etc.), sampling media (e.g., nature of sorbent in absorbers, liquids in impingers), types of pumps, positioning and flow rates, if appropriate, must be specified. For dermal exposure, the method for measuring hand exposure (gloves, hand rinse, etc.) must be specifically described, as well as the types of dosimeters to be used for evaluation of the other parts of the body. If the patch method is to be used for dermal exposure evaluation, the number and locations of the patches must be indicated, including whether patches are to be placed inside or outside normal clothing, or both. If biomonitoring is to be employed, the procedures and rationale should be described in detail.

Critical factors that may need to be addressed in the selection of monitoring methods include:

- The environmental fate and/or transport characteristics of the active ingredient;

- Major pathways through which the pesticide may degrade or dissipate; and

- The durability of dosimeters and sample collection devices; they must be designed to: (1) survive the duration of the monitoring effort; (2) be the most appropriate for the pesticide; (3) avoid overloading during the collection period; and (4) survive storage and shipment to the analytical laboratory and not have losses of residues due to the storage containers (e.g., leaching of residues into matrix of plastic bag).

- The need to change clothing, gloves, or samples, or wash hands during the workshift in case of breakthrough or to coincide with natural breaks in the day.

2.6 SAMPLE HANDLING AND COLLECTION PROCEDURES

Defining sample collection procedures prior to initiating the field phase of any study ensures added integrity for the samples. It also lowers the risk to the investigators of study failure due to unforeseen analytical problems. The study design should provide a description of:

- The preparation of sampling devices prior to the conduct of the study;
- The sample collection procedures to be employed;
- The methods and precautions to be used in removing samplers from workers; and
- Storage and shipment procedures to be employed.

- Select sample storage vessels that allow for quantitative transfer of residues into an extraction vessel or that serve as the extraction vessel itself.

2.7 ANALYTICAL CHEMISTRY

In the study design the study investigator should briefly describe which analytical methods will be used to measure the analyte(s) of concern. Also, the study investigator should indicate (if known) the stability of the analyte and describe how the stability of each analyte under investigation will be verified. Finally, in the study design the study investigator should indicate the proposed limits of quantitation for each analyte. Described in Part C are specific analytical routines for characterizing the stability of the analyte and more information on providing and determining the limits of quantitation.

2.8 QUALITY ASSURANCE AND QUALITY CONTROL

The data collected in a study should be of sufficient quality and quantity to support defensible decisionmaking, especially for critical measurements needed to meet project objectives. In designing any study, QA/QC measures must be built into the study early in the process. Inherent to the QA/QC process is the development of Data Quality Objectives (DQOs). The DQO process, a systematic planning tool for establishing criteria for data quality and for developing data collection designs, assures that the type, quantity, and quality of environmental data used in decisionmaking will be appropriate for the intended application. DQOs are qualitative and quantitative statements that clarify the study objectives, define the most appropriate type of data to collect, determine the most appropriate conditions for data collection, and specify tolerable limits on decision errors. Performance requirements are established before the study begins by considering the consequences of decision errors and setting tolerable limits; and the data collection design is based on these criteria. Additional information on the DQO process may be found in EPA guidance (U.S. EPA, 1994).

Generally, quality assurance provides the user of data assurance that it meets defined standards of quality with a stated level of confidence (Taylor, 1987). Precision, accuracy, completeness, representativeness, comparability, and detection limits may be used as indicators of data quality. The DQO System provides the basis for linking the intended use of the data to the QA/QC requirements for data collection and analysis.

2.8.1 Quality Assurance

Quality assurance requirements may be found in the Good Laboratory Practice (GLP) Standards (U.S. EPA, 1989). These regulations "define the function of the quality assurance unit (QAU) in regulated studies as that of ensuring managers that all aspects of the facility, personnel, performance, record-keeping, and reporting are consistent and in compliance with the regulations. The objective of the regulations is to ensure users...of (the generated) information...of accuracy and to ensure integrity of study conduct and reported results according to specifications in the GLPs. This objective is achieved through the development of quality assurance programs that systematically evaluate and monitor...studies, as well as the activities of the facility and personnel."

Consideration of Good Laboratory Practices. The provisions of the Good Laboratory Practice Standards are intended to assure the quality and integrity of data submitted to the Agency (U.S. EPA, 1989). In conducting a study and submitting the data, the investigator must consider the provisions of the GLP standards. Some highlights of the GLP standards that are particularly applicable to postapplication exposure studies include:

- Test Substance Characterization (40 CFR 160.105). Test substances used in studies must be characterized according to the Good Laboratory Practices (GLPs) presented in 40 CFR 160. The investigator should characterize materials PRIOR to performing field trials. Aliquots of the test substance(s) should be retained during field trials for analysis, if any questions arise regarding the validity of the test substance(s). Test substance(s) include for the purposes of Series 875 Group B any materials containing the pesticide(s) of interest used in field trials or sample analysis.

- Protocol Requirements (40 CFR 160.120). The GLPs require that "each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study." Each protocol should contain the following: a title and statement of purpose; identification of the test, control, and reference substances; names and addresses of the sponsor and performing laboratory; proposed experimental start and termination dates; justification for selection of test system; procedure for identification of the test system; a description of the experimental design; a description of the materials used to solubilize or suspend the test, control, or reference substances before mixing with the carrier; the route of administration and the reason for its choice; dosage level (i.e., application rates); sponsor approval dates and study director signature date; a statement of proposed statistical method; and signed protocol amendments.

- Sample Receipt, Handling, and Tracking (40 CFR 160.130). Critical to the success of any laboratory operation are the sample receipt, handling, and tracking procedures. Each sample must be identified with an individual code number. Sample receipt and storage inventories must also be maintained in accordance with the GLPs. Storage facilities must be maintained at constant temperatures. Daily records must be collected to verify conditions. Sample shipments must be made using the most expeditious and appropriate method to ensure the integrity of the field samples. Laboratory operations should maintain Standard Operating Procedures (SOPs) for the operations described above.

- Sample Storage (40 CFR 160.41). As soon as samples reach the laboratory from the field, all samples held in ice chests must be stored in a refrigerator or freezer, as appropriate, pending further treatment. A sample history sheet should be prepared to document laboratory operations. A convenient sheet of this type contains columns labeled: sample number, date sample was collected, date of extraction, date of analysis, and the name(s) of the individual(s) responsible for the task. The lower portion of the sheet contains spaces for recording the conditions of storage for pads, other matrices, extracts, the extraction procedure employed, and the analytical procedure used.

In a study design expected deviations from GLPs need to be listed and discussed. GLP deviations should be presented concurrently with any protocol deviations along with their potential study impacts as required in the GLPs.

2.8.2 Quality Control

Appropriate quality control procedures are critical to the successful completion of any study conducted under these guidelines. Investigators are encouraged to refer to Part C - Quality Assurance/Quality Control for detailed guidance pertaining to the development of a study protocol, issues pertaining to field sampling procedures, and issues pertaining to residue chemistry.

2.9 CONTINGENCY PLANNING

The study design should include contingency plans for major weather events, attrition of study participants (e.g., due to heat exhaustion), or other circumstances that may adversely affect successful study completion.

2.10 REPORTING AND RECORD KEEPING

Study reports should contain the types of information described in this section as well as the justification for each aspect of the study. The interpretation of study results depends upon the understanding provided in the report concerning the study design (e.g., the rationale used for site selection and the identification of activities to be monitored are critical to interpreting the study). Data used in developing a technical approach and any decisions based on best professional judgment should be documented in study reports. Any *Confidential Business Information (CBI)* as stipulated under Section 106 of FIFRA should be clearly noted and claimed as CBI as described in FIFRA submission instructions to the Agency (FIFRA, 1988).

REFERENCES FOR PART B, CHAPTER 2

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PART B - CHAPTER 3

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PART B - CHAPTER 3
DISLODGEABLE FOLIAR RESIDUE DISSIPATION: AGRICULTURAL GUIDELINE 875.2100

3.1 INTRODUCTION

This Guideline provides a description of the techniques and sampling strategies commonly used to characterize dislodgeable foliar residue (DFR) dissipation. Such dissipation data are used in conjunction with concurrent human exposure data to establish chemical transfer coefficients, to determine restricted-entry intervals, and to evaluate risks associated with postapplication exposure to pesticides. DFRs represent chemical residues on the surfaces of treated foliage that are available for transfer to exposed populations (e.g., reentry workers) during contact with those treated leaf surfaces. That is, DFRs are the amount of chemical residues deposited onto the leaf surface that have not been absorbed into the leaf or dissipated from the surface, and that can be dislodged by shaking leaf samples in a detergent solution. (See Gunther et al., 1973.)

3.2 SAMPLE COLLECTION

3.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

3.2.2 Timing of Application

Sample collection should be conducted during the intended use season or under climatic conditions that are essentially identical to those encountered during the intended use season. Weather forecasts should be studied to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. For further information on climatological considerations, see Part B, Chapter 2 - Study Design.

3.2.3 Pesticide Application Rate and Frequency

Generally, the end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate, if possible. For example, typical rates are often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will also provide additional information about the relationship between the application and deposition rates. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptabie risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, testing at a longer time interval between applications may prove to be beneficial if unacceptable risks were to result. Registrants should note, however, that if the maximum rates or minimum application intervals are not monitored, subsequent label changes may be necessary. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance should be used.

3.2.4 Sampling Parameters

The following paragraphs provide a description of: where geographically sampling should occur (i.e., site selection); how long the dissipation must be characterized (i.e., the sampling period); the times within the sampling period that samples should be taken (i.e., sampling intervals); and the number of samples that should be taken at each sampling interval along with a description of where at the sampling location to sample.

3.2.4.1 *Number of Geographic Locations*

In general, DFR samples are typically collected from at least three geographically distinct locations per formulation type. This is usually necessary to ensure that varying climatic conditions, crops, and pest types are represented. (See Chapter 2, Study Design, for more guidance.)

3.2.4.2 *Sampling Period*

Data should be collected in a manner that characterizes the dissipation mechanisms for the compound (e.g., three half-lives). Further, the sampling period should be reflective of the exposure conditions and toxicological endpoint of concern (i.e., acute or chronic). Typically, DFR dissipation rates are characterized for at least 35 days postapplication for agricultural sites unless the compound has been found to fully dissipate in less than this time period. EPA has observed that this sampling period is usually adequate for characterizing pesticide dissipation under most use conditions; for most pesticides, significant dissipation occurs within the first week of application. Please note, however, that for more persistent pesticides a longer sampling period may need to be used.

3.2.4.3 *Sampling Intervals*

Generally, the length of time between sampling should be relatively short in the beginning and should lengthen as the study progresses. EPA recommends that samples be collected prior to application on the day of application; on the application day at various hourly intervals after application (e.g., 4 hours or 12 hours after application may be appropriate); and on various days postapplication. For example, sampling at 1, 2, 4, 7, 10, 14, 21, 28, and 35 days after application may be appropriate. Please note that for certain pesticides (e.g., one that degrades quickly) shorter sampling intervals may suffice. However, sampling should continue for 35 days, but all of the samples may not need to be analyzed if the pesticide has fully dissipated (i.e., nondetects for two sampling intervals). On the other hand, sampling may need to continue beyond 35 days for more persistent pesticides. Special consideration should also be given to pesticides that exhibit biphasic dissipation kinetics.

If typical chemical use patterns involve a sequential series of treatments (i.e., multiple applications), samples in addition to the ones indicated above should be collected. Generally for multiapplication scenarios, the Agency recommends that samples be collected prior to and after each application on the day of application. Additionally, after all but the final applications (see above), samples should be collected at least every 7 days after each application during the intervals between application events (e.g., if multiple applications occur on a 14 day interval, then samples should be collected prior to and after each application and 7 days after each application). However, modifications to this sampling scheme may be proposed to the Agency if the market and use pattern will accept that reentry is prohibited between applications, or if the registrant is willing to accept the results and restrictions imposed by the alternative sampling scheme.

The proposed sampling intervals should be presented to EPA for review in the study protocol prior to initiation of the study to ensure that they are agreeable to the Agency.

3.2.4.4 *Number of Samples and Sampling Positions*

The Agency recommends that at least three samples be collected at each sampling interval. Each of the replicate samples should be taken from different areas within the treated location. Sampling should occur in the worker contact zone (i.e., in those areas where workers will be conducting their activities). Several approaches have been utilized by investigators to determine where to sample within treated areas. These include, but are not limited to: nondirected sampling; the Iwata approach for tree crops (Iwata et al., 1977); and the planned approach for row crops. Control plots should also be established. Sufficient control samples should be collected to ensure that the same bulk sample can be used as a negative control matrix throughout all sample analyses. Additionally, samples from the control plots should be collected at each interval for assessment of the field sample collection and storage procedures.

In nondirected sampling, field technicians enter a treated area and sample at their own discretion. The Iwata approach provides guidance for collecting DFR samples from tree crops. Samples are collected at 45 degree intervals around the circumference of each sampled tree and at varying heights in the tree (see Figure B3-1). In the planned approach, investigators develop a scheme that predetermines sample collection locations (see Figure B3-2). EPA recommends that a planned approach be used for DFR sample collections for typical field crops (e.g., row crops such as strawberries or tomatoes) and that the Iwata approach be used for tree crops.

3.2.5 Technique Validation

The concept of dislodgeable foliar residue sampling is based on the assumption that available residues are removed from the surface of treated foliage by washing (i.e., dislodging) with an aqueous surfactant solution. However, data are not available to quantify the actual rate of transfer from the treated surface into solution (i.e., no mass balance data are available). As a result, the only validation that is routinely required by the Agency is to determine the efficiency of extraction of the chemical residue(s) of concern from the dislodging solution and the stability of those residues in the solution over time if sample storage is required prior to analysis. No further validation data are required until a technique becomes available to accurately quantify the mass balance (i.e., efficiency of the dislodging procedure).

3.2.6 Sampling Techniques

There are two types of approaches for monitoring dislodgeable foliar residue levels (i.e., leaf punch and whole leaf sampling). The equipment required for each approach is described below. For all studies, a leaf punch apparatus should be used unless the nature of the crop (e.g., small leaves) precludes its use. Additionally, aqueous dislodging solutions should be used.

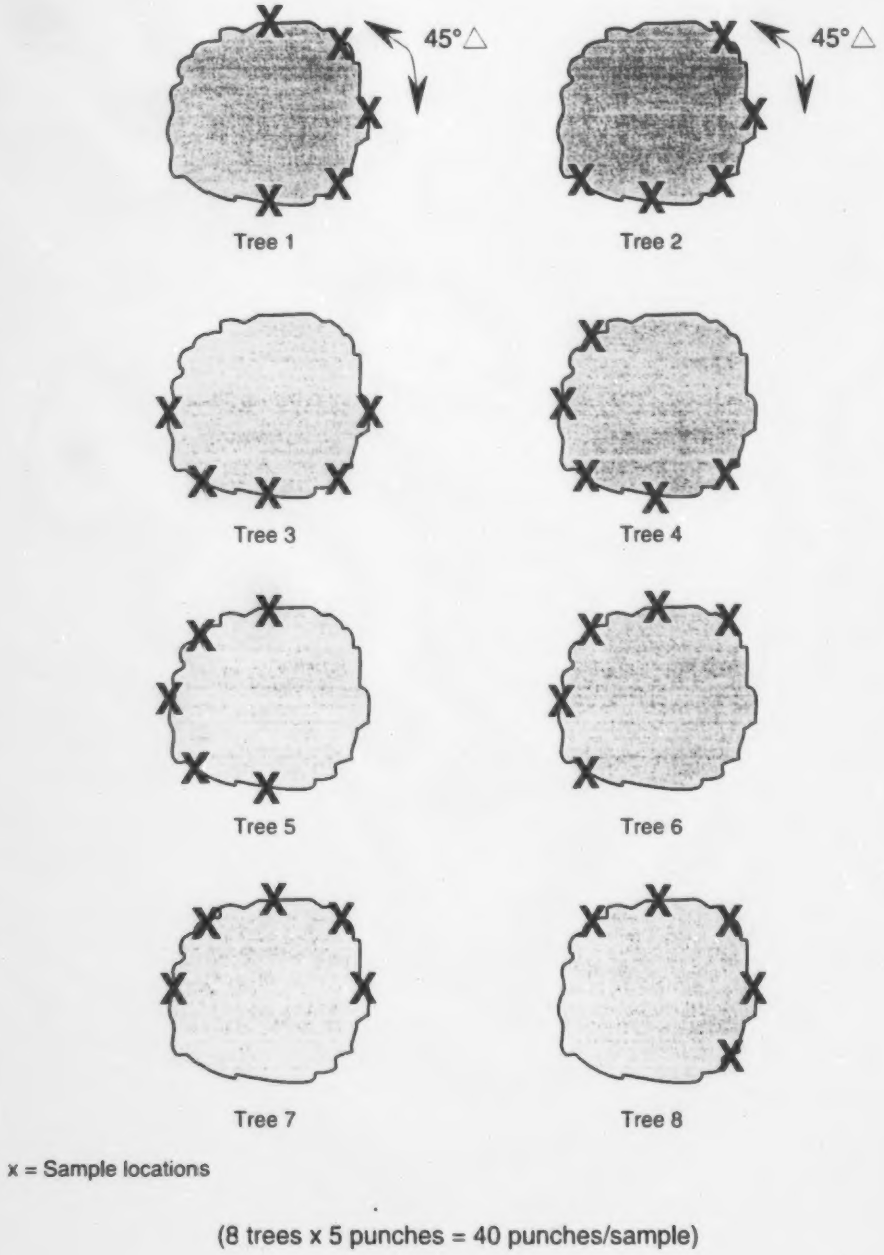
45°△
45°△
Tree 1
Tree 2
Tree 3
Tree 4
Tree 5
Tree 6
Tree 7
Tree 8
x = Sample locations
(8 trees x 5 punches = 40 punches/sample)

Figure B3-1. IWATA Approach for Tree Crop Sampling

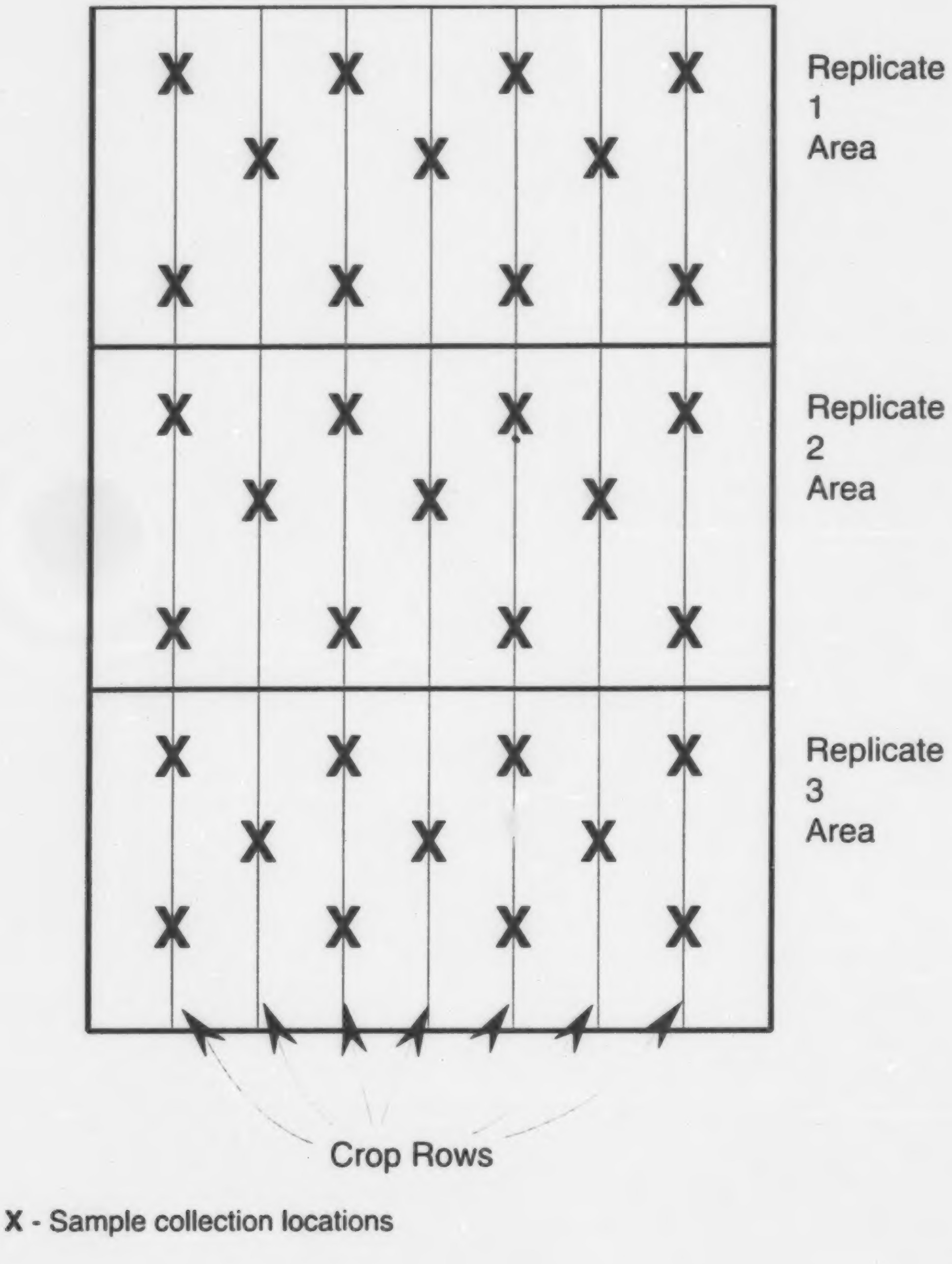
Replicate 1 Area
Replicate 2 Area
Replicate 3 Area
Crop Rows
X - Sample collection locations

Figure B3-2. Planned Approach for Field Crop Sampling

3.2.6.1 *Leaf Punch*

The leaf punch apparatus is a device that enables investigators to collect DFR samples in a systematic, reproducible manner. A typical leaf punch is a machined tool that consists of a rigid handle to which a trigger mechanism is attached that can depress a round punch of known surface area against a fixed, round blade (Figure B3-3). Three leaf punch sizes are generally available: 1/4, 1/2 and 1-inch diameter punches (i.e., approximately 2.5, 5.0, and 10 cm^2 double-sided surface area). Sampled leaf surfaces are placed between the round punch and the blade. As the trigger mechanism is depressed, round leaf samples of known surface area (herein referred to as leaf punches) are collected for analysis in a vessel affixed to the rigid handle of the leaf punch apparatus below the round blade (e.g., glass jar sealed with a Teflon-lined cap). Leaf punches should be used by investigators whenever possible. Generally, the size and shape of the target crop of interest determines whether or not a leaf punch is feasible for DFR sampling. For example, a leaf punch may not be appropriate for small, oddly shaped foliage. Also, leaf punches may be inappropriate when the active substance is absorbed into the plant fluids. Such fluids become available through the relatively high amount of cuts in the leaves. The advantage of using the leaf punch approach is that samples of known surface area may be collected.

3.2.6.2 *Whole Leaf*

For scenarios in which the use of a leaf punch is not feasible, whole-leaf samples must be collected. Leaves should be plucked from the target plants using forceps and placed into a sample storage vessel (e.g., glass jar sealed with a Teflon-lined cap).

In cases where whole-leaf sampling is required, a technique must be devised to determine the foliar surface area of each DFR sample. Sample surface areas may be calculated by determining the weight of each DFR sample and multiplying these weight values by a ratio or algorithm that relates surface area to sample weight on a unit basis. (See Part D, Chapter 2.) It is acceptable to make these determinations using fresh control samples prior to sampling in the field if the plant materials used to make the determinations are generally similar to those in the study (e.g., similar maturity leaves). The equipment and techniques used to determine unit target leaf area values are varied. Surface area meters are commercially available that are designed specifically for this purpose. These devices function based on the principle of absorbance, similar to the application of the principle in UV/Vis meters commonly found in most chemistry laboratories. (See Figure B3-4.) Less sophisticated, labor intensive hand techniques have also been used by investigators (e.g., copying representative leaves, cutting out the copied leaves, and relating the weight of the cut-outs to that of the paper on a unit basis).

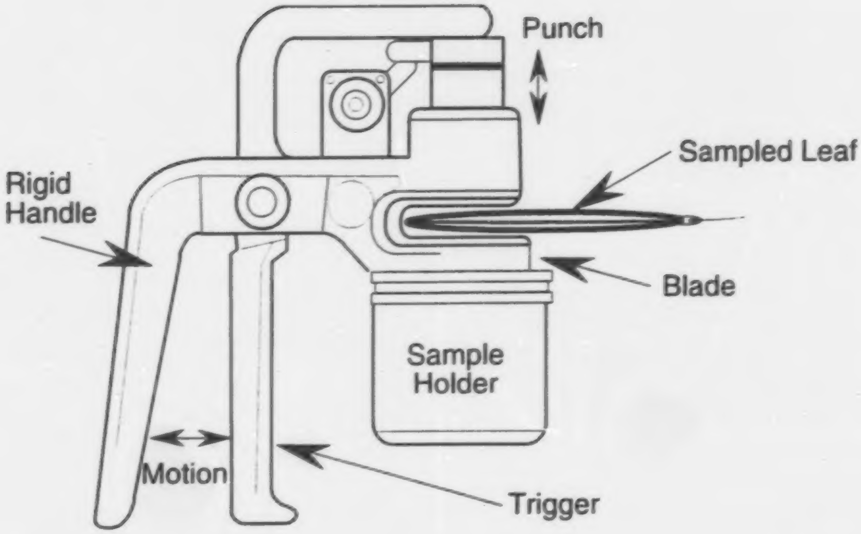
Punch
Sampled Leaf
Rigid Handle
Blade
Sample Holder
Motion
Trigger

Figure B3-3. Schematic of a Typical Leaf Punch Apparatus

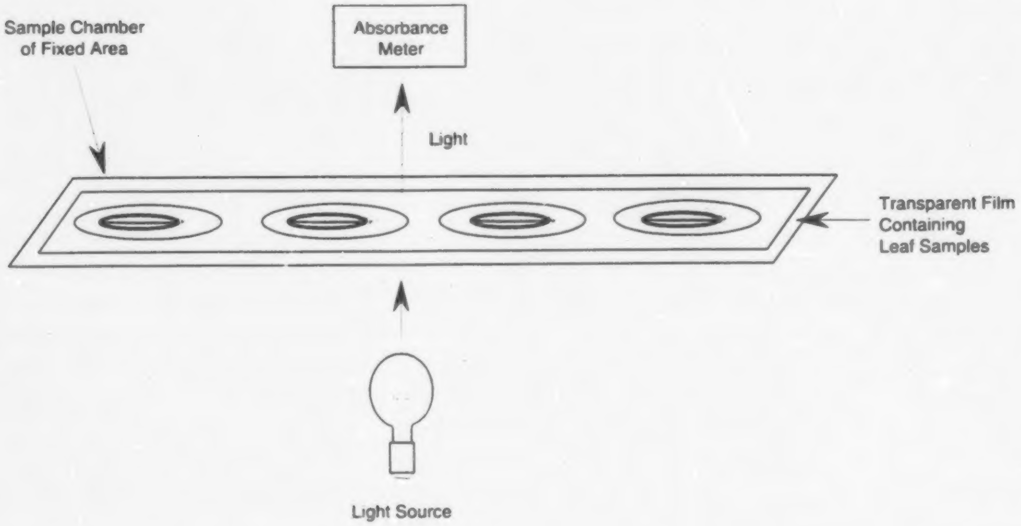
Sample Chamber of Fixed Area
Absorbance Meter
Light
Transparent Film Containing Leaf Samples
Light Source

Figure B3-4. Schematic of a Typical Surface Area Meter

Other equipment/techniques may also prove to be viable options for quantifying the relationship of leaf surface area to weight. If an alternative technology is used for this determination, investigators must demonstrate the validity of the technique for determining surface area to weight relationships.

3.2.7 General Considerations for Field Sample Collection

Collecting samples that represent an adequate leaf surface area is critical in any DFR study. Generally, all replicate samples that are collected should represent at least a surface area of 400 cm^2, based on a double-sided leaf area. Double-sided leaf area represents the surface area on both sides of individual leaf-punches or whole-leaf samples (e.g., 1-inch diameter leaf punch represents a double-sided surface area of 10 cm^2). Determination of the required surface area is a simple task if the investigator is using a leaf punch device to collect samples. (See Figure B3-3.) As an example, if a 1-inch diameter leaf punch is being used to collect samples, then at least 40 punches must be included in each sample (i.e., approximately 10 cm^2 x 40 punches/sample). Most leaf punches are equipped with automatic counters to ease the sample collection process. If the whole-leaf sampling method is required for the particular target/crop, investigators must have a knowledge of the surface area to weight ratio for that crop along with some idea of how many leaves represent 400 cm^2 prior to going in the field. The Agency recognizes that investigators using this technique may not always collect samples that represent a sufficient surface area due to the subjectivity involved in sample collection.

Control or background samples should be collected from the test plot prior to application of the test substance. Sufficient control samples should be collected so that fortified dislodging solutions that have been used to wash control leaves can be prepared on each sampling day. These fortified controls should be packaged, transported, stored, and analyzed concurrent with the dislodgeable residue samples. Please see Part C for detailed considerations on Quality Assurance and Quality Control recommendations.

3.2.8 Sample Dislodging Procedures

Dislodgeable foliar residues (DFRs) are those residues present on the surface of a leaf that are available for transfer from the leaf (i.e., residues that have not been absorbed into leaf matrix). DFRs are quantified by washing (i.e., consistently shaking for a set period of time, for example, roughly 10 minutes) chemical residues from the surfaces of leaves using some type of dislodging solution. Generally, the dislodging procedure involves preparing an aqueous surfactant solution, adding an aliquot to each replicate leaf punch sample, shaking the mixture, and retaining the solution for analysis. This procedure should be repeated at least once to ensure a more quantitative residue transfer during the dislodging procedure. The resultant dislodging solutions should be pooled for analysis as one sample. A sufficient quantity of dislodging solution should be used during each step of the procedure to adequately cover the leaf punches/samples to ensure that the agitation is efficient during the shaking aspect of the procedure.

Aqueous surfactant solutions similar to that proposed by Iwata et al. (1977) are commonly used as dislodging solutions. The procedure proposed by Iwata et al. (1977) was based on the use of an aqueous surfactant solution prepared by adding 4 drops of a 1:50 dilution of Sur-Ten wetting agent into 100 mL of water. Sur-Ten is 70 percent dioctyl-sulfosuccinate sodium salt. A variety of other types of dislodging solutions have also been used (i.e., other surfactants have been used at varying concentrations in different dislodging solution volumes). The Agency has no data to suggest that one aqueous surfactant solution is preferable to another (i.e., at this point any reasonable aqueous surfactant solution is acceptable to the Agency). Investigators have also, in some cases, used organic solvents as dislodging solutions (e.g., ethanol or methanol). However, the use of organic solvents is considered unacceptable by the Agency as these types of solvents may actually extract residues from the leaf matrix itself and not just from the surface of the leaf. Therefore, the results using organic solvents would not be representative of a true DFR.

The Agency recognizes that the use of aqueous foliar dislodging solutions may not be appropriate for all chemicals because of their physical/chemical characteristics (i.e., water solubility). Investigators should consider these characteristics when selecting a dislodging solution.

The determination of an acceptable interval between field sample collection and the actual dislodging procedure is difficult. Therefore, as a protective measure, the Agency recommends that all DFR samples be dislodged within approximately 4 hours of field sample collection (frequently, this is done in the field). This recommendation may be modified on a case-by-case basis, if available data (e.g., environmental fate or product chemistry) or logistical considerations warrant. Most studies that have been completed to date comply with this recommendation. However, several studies have been submitted to the Agency in which the leaf punches were not dislodged for days or even months after sample collection. A study of this nature would most likely not be acceptable to the Agency as the potential exists for DFR absorption into the leaf matrix during storage, thereby, potentially reducing the measured DFR levels.

Another parameter that may significantly impact DFR results is the method of agitation. Historically, two methods of agitation have been employed by investigators: hand shaking and agitation using a mechanical, reciprocal shaking table. The Agency has no data on the advantages and disadvantages of these two methods. Until such data become available to indicate a preference for either method, the Agency will accept the use of either technique in a DFR study. However, investigators must attempt to develop procedures that are as reproducible as possible (e.g., consistently use a reciprocal shaker for 10 minutes at a specified speed or hand shake each sample for 10-minute intervals).

3.2.9 Unit Surface Area Determination

The determination of unit leaf area factors is necessary when the use of a leaf punch apparatus is not feasible. As described above, several types of equipment are available for quantifying this relationship. In all cases, regardless of the equipment/technique selected, the Agency requires that multiple samples be collected and that all analyses be done on a wet weight basis (i.e., extra leaf samples are to be collected for surface area measurements only from the study site). Investigators must ensure that leaf samples used for surface area determinations are not dehydrated, thus altering the relationship between surface area and weight. Preventing dehydration can be accomplished by conducting the surface area analysis within 4 hours (i.e., fresh samples) after harvesting the leaf samples. The surface area determinations may be conducted prior to the study. The Agency requires that a minimum of four replicate samples for at least three distinct theoretical weights be analyzed to define the relationship (i.e., a minimum of 12 samples are required for each surface area to weight analysis). Theoretical weight can be defined as a target weight for preparing each replicate sample, keeping in mind that variations in individual leaf samples will preclude the exact target weight from being met for most samples. However, investigators should attempt to keep actual samples weights within ± 5 percent of the target weight. The three target weights used by investigators should be defined based on the following: 75 percent of the anticipated field weight; the anticipated sample weight; and 125 percent of the anticipated sample weight. The anticipated sample weight can be defined as the anticipated weight of each sample intended for DFR analysis collected in the field (i.e., target weight for field samples that represents the required leaf surface area/sample -- 400 cm^2 per sample, at a minimum, as described above).

3.3 SAMPLE STORAGE

Dislodgeable foliar residue samples and extracts should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis; more detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. Also see Residue Chemistry Methods 860.1340 (Subdivision O) for more information. The study investigator is responsible for demonstrating the stability of the samples under the storage duration and conditions used.

3.4 SAMPLE ANALYSIS

Pesticide residues should be dislodged from leaves within 4 hours of sample collection. Validated methods of appropriate or sufficient sensitivity are needed for all sample analyses. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

3.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates, exposure, and risk.

3.6 DATA PRESENTATION

Dislodgeable foliar residues should be reported as mg or μg of pesticide active ingredient per m^2 or cm^2 of leaf sampled. These data should be reported in tabular form for each sampling day. In addition, the best fit dissipation curve should be plotted (typically log-linear) with dislodgeable foliar residues on the Y-axis and time on the X-axis. Distributional data should be provided, to the extent possible.

REFERENCES FOR PART B, CHAPTER 3

Gunther, F.A.; Westlake, W.E.; Barkley, J.H.; Winterlin, W.; Langbehn, L. (1973) Establishing Dislodgable Pesticide Residues on Leaf Surfaces. Bull. Environ. Contam. Toxicol. 9:243-249.

Iwata, Y.; Knaak, J.B.; Spear, R.C.; Foster, R.J. (1977) Worker Reentry into Pesticide Treated Crops, In: Procedure for the Determination of Dislodgable Residues on Foliage. Bull. Environ. Contam. Toxicol. 18:649-655.

U.S. EPA. (1997) Standard Operating Procedures (SOPs) for Residential Exposure Assessments, draft report. Washington, D.C.: U.S. Environmental Protection Agency, Office of Pesticide Programs.

PART B - CHAPTER 4

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PART B - CHAPTER 4
TRANSFERABLE RESIDUE DISSIPATION: LAWN AND TURF
GUIDELINE 875.2100

4.1 INTRODUCTION

This Guideline provides a description of the techniques and sampling strategies commonly used to characterize pesticide dissipation on lawns and turf. Such dissipation data are used in conjunction with concurrent human exposure data to establish chemical transfer coefficients which in turn are used to determine restricted-entry intervals for agricultural situations (e.g., sod farms). Further, for turf pesticides, characterizing residue dissipation rates provides valuable information for posting and notification requirements, where applicable. Lawn surface residue data are also used to determine whether or not a given pesticide may be used without appreciable risk in a residential setting.

4.2 SAMPLE COLLECTION

4.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

In choosing the typical end-use product, factors to consider include (but are not limited to): formulation, irrigation practices (i.e., "watering in"), and concentration of active ingredient in the spray solution. For example, several researchers have found that lawn surface residues are greater following applications of liquid formulations than after granular application (Sears et al., 1987; Cowell et al., 1993). Therefore, for a pesticide available in several different formulations, a liquid formulation (e.g., emulsifiable concentrate) should be chosen for testing. Furthermore, it has been demonstrated that "watering in" immediately after application may move pesticide residues into the thatch where they are less available (Niemczyk and Krueger, 1987). Therefore, a product for which "watering in" is not prescribed for efficacy should be selected for testing. Similar to "watering in," applying a pesticide in a large volume of water may carry the residues into the thatch. Therefore, products which can be applied in a minimal amount of water should be used.

4.2.2 Timing of Application

Sampling should be conducted during the intended use season or under climatic conditions that are essentially representative of those encountered during the activity being studied. Applications should be made after mowing and watering. Weather forecasts should be studied, as much as possible, to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. (See Part B, Chapter 2 - Study Design for more information.)

4.2.3 Pesticide Application Rate and Frequency

Generally, the end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate, if possible. For example, typical rates are often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will also provide additional information about the relationship between the application and deposition rates. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, testing at a longer time interval between applications may prove to be beneficial if unacceptable risks may result. Registrants should note, however, that if the maximum rates or minimum application intervals are not monitored, subsequent label changes may be necessary. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance and intended end-user (i.e., private resident versus commercial lawn care applicator) should be used.

4.2.4 Sampling Parameters

The following paragraphs provide a description of: where geographically sampling should occur (i.e., site selection); how long the dissipation must be characterized (i.e., the sampling period); the times within the sampling period that samples should be taken (i.e., sampling intervals); and the number of samples that should be taken at each sampling interval along with a description of where at the sampling location to sample.

4.2.4.1 *Number of Geographic Locations*

Samples are typically collected from at least three geographically distinct locations per formulation type. This is necessary to ensure that varying climatic conditions, crops, and pest types are represented. For the purposes of selecting these locations for a study, investigators should consider differences in species, climate, and cultural practices within different geographic regions. For example, St. Augustine grass in Florida has a different growth habit than Kentucky Bluegrass in Missouri, or Bermuda grass in California. In addition, the amounts of rainfall, air and soil temperatures, mowing intervals, and other factors differ within these regions. (See Chapter 2, Study Design, for more guidance.)

4.2.4.2 *Sampling Period*

Data should be collected in a manner that characterizes the dissipation mechanisms for the compound (e.g., three half-lives). Further, the sampling period should be reflective of the exposure conditions and toxicological endpoint of concern (i.e., acute or chronic). Typically, dissipation rates are characterized for at least 72 hours postapplication unless the compound has been found to fully dissipate in less than this time period. EPA has observed that this sampling period is usually adequate for characterizing pesticide dissipation under most use conditions. Please note, however, that for more persistent pesticides, a longer sampling period may need to be used. In addition, the recent passage of the Food Quality Protection Act may result in the need for monitoring over longer periods to allow for the aggregation of long-term exposures from multiple sources (i.e., dietary plus dermal). Registrants should present the proposed sampling period in the study protocol prior to initiation of the study to ensure that it is agreeable to the Agency.

4.2.4.3 *Sampling Intervals*

Generally, the length of time between sampling days should be relatively short in the beginning and should lengthen as the study progresses. EPA recommends that samples be collected prior to application on the day of application; and on the application day at various intervals after application. For example, sampling at 1, 4, 8, 12, 24, 48, and 72 hours after application may be appropriate for residential turf. Please note that for certain pesticides (e.g., one that degrades quickly) shorter sampling intervals may suffice. However, the sampling should continue for 72 hours, but all of the samples may not need to be analyzed if the pesticide has fully dissipated (i.e., nondetects for two sampling intervals). On the other hand, sampling may need to continue beyond 72 hours for more persistent pesticides. Special consideration should also be given to pesticides that exhibit biphasic dissipation kinetics.

The proposed sampling intervals should be presented to EPA for review in the study protocol prior to initiation of the study to ensure that they are agreeable to the Agency.

4.2.4.4 *Number of Samples and Sampling Positions*

The Agency recommends that at least three samples be collected at each sampling interval. Each of the replicate samples should be taken at random from different areas within the treated location. For example, on a given lawn, the triplicate samples should be collected to account for differences in turf density, pesticide application variation, and environmental factors. Control plots should also be established. Sufficient control samples should be collected to ensure that the same bulk sample can be used as a negative control matrix throughout all sample analyses. Additionally, samples from the control plots should be collected at each interval for assessment of the field sample collection and storage procedures.

4.2.5 Sampling Techniques

The measurement of lawn surface residues is a relatively new area in the field of exposure assessment. The various techniques that have been employed by researchers since the early 1980s are mostly modifications of agricultural dislodgeable residue techniques or techniques being developed for indoor surface sampling.

Presently, EPA does not have sufficient information to recommend one sampling technique as a better measure over the others. However, with the research currently underway, the Agency will continually improve its ability to assess each method. As research on the following methods (especially as they apply to lawn surface residue sampling) is an ongoing effort within EPA and the chemical industry, the importance of reviewing the most recent published literature before selecting a method cannot be over emphasized. Regardless of the residue sampling method selected, a relationship must be proposed between the residue data and dose during one or more defined activities. Such a relationship is usually obtained via the transfer coefficient generated from the concurrent collection of residue and exposure data, as described in Part B, Chapters 7 through 10. Also, study investigators are encouraged to propose new methodologies for estimating exposure from lawn surface residues and to validate existing methods. The selected methods must satisfy specific performance criteria as described in Part C, Quality Assurance and Quality Control.

The following is a brief description of each available method. Detailed descriptions of these methods may be found in the literature and in "Methods for Assessing Residential Exposure to Pesticides," (U.S. EPA, 1994).

4.2.5.1 *Dislodgeable Residue Technique*

In the dislodgeable residue technique, all grass is obtained from randomly selected defined areas of the treated plot. The grass clipping samples may be weighed, but the residues must be dislodged in the field within 4 hours of sampling. The residues are dislodged by washing (i.e., consistently shaking for a set period of time, for example 10 minutes) the grass clippings in a detergent or surfactant solution (see Section 3.2.8 for further details) (Goh et al., 1986a; Goh et al., 1986b). Prior to the study, multiple grass clipping samples (a minimum of three samples) must be obtained from the test plot to establish a correlation between leaf surface area and weight. This correlation is established by weighing fresh grass clippings that have been placed on a template of known surface area. Multiple surface areas (and, therefore, multiple weights) must be tested to establish the correlation. The weights tested should bracket the anticipated sample size for the dislodgeable residue testing. While determining the weight/surface area correlation, it may be necessary to correct for moisture losses occurring while grass leaves are being arranged on the templates (Hurto and Prinster, 1993). Refer to Part B, Chapter 3 for further information on DFR dissipation study techniques.

4.2.5.2 *Cheese Cloth Wipe Technique*

There are various approaches to wipe techniques for determining transferable lawn surface residues. One technique described in the published literature involves a person scuffling forward and backward over a designated area of treated turf (Sears et al., 1987). More specifically, the sampler dons a pair of boots. The boots are then covered; first with protective plastic and then with multiple layers of cheese cloth that have been moistened with distilled water. Another technique that may provide better reproducibility is to use platforms (e.g., cooking pans) attached to the bottom of the feet. The sampling material (e.g., cheese cloth) can be attached to the underside of the platforms. The spreading of weight allows for greater distribution of weight (i.e., less pressure) and more uniform results among investigations. The sampler then scuffles forward and backward over a 1 m^2 area for a specified amount of time (e.g., 1 minute). One replicate consists of triplicate samples (i.e., three 1 m^2 samples) per sampling interval. The cheese cloth is then removed from the sampler, the excess, unexposed material is cut away, and the remainder is transported, on ice, to the laboratory for extraction and analysis.

4.2.5.3 *Polyurethane Foam Roller*

The polyurethane foam roller (PUF roller) was designed to measure transferable residues from contaminated surfaces that a child may contact during various activities (i.e., crawling) (U.S. EPA, 1994; Hsu et al., 1990). Originally, the device was designed and tested on indoor surfaces (e.g., vinyl flooring). More recently, the design of the PUF roller has been altered to facilitate use on turf. (See

Figure B4-1.) In general, the PUF roller device consists of a PUF ring (8.9 cm outside diameter x 8 cm long) that is fitted around an aluminum or stainless steel roller. This roller is attached to the end of a wheeled, forked handle. The device is weighted (via the stainless steel roller or weights attached to the forked handle) to exert a pressure of 7,300 Pa while rolling (approximating the pressure of a crawling or standing child). The roller is pushed over a specified area of treated turf to sample for surface residues. After sampling, the PUF ring is transported, on dry ice, to the laboratory for extraction and analysis. To simulate the moistness of the human skin, the PUF may be moistened with water.

4.2.5.4 *California Cloth Roller*

As is the case for the PUF roller, the California cloth roller was originally designed to measure residues that may be dislodged by a child in contact with indoor surfaces (U.S. EPA, 1994; Ross et al., 1990). (See Figure B4-2.) However, this sampling technique may be applied to turf with minimal modifications. In general, a sheet of percale cotton/polyester cloth is placed over a specified area of the treated lawn. A sheet of protective plastic (or clean cotton toweling) is then placed over the cloth. When the sheets are in place, a weighted foam covered roller (similar to a baker's rolling pin or a paint roller) is rolled over the entire covered area 10 times. The percale cloth is then collected and transported to the laboratory, on ice, for extraction and analysis.

Recently, the Outdoor Residential Exposure Task Force developed a modification of the California Cloth Roller technique for use outdoors on turf (Johnson, 1998). The roller is a 4-inch diameter by 24-inch long PVC pipe. The outside of the roller is wrapped with half-inch polyurethane foam sheet, or equivalent pipe insulation, for cushioning and traction. Enough weight is added to the inside of the roller to bring the total weight (excluding the handle) to 32 pounds, which is evenly distributed across the length of the roller. A handle is added to the roller. A rectangular-shaped frame is made of PVC material with inside dimensions of 24.5 x 36 inches. A 27 x 39 inch piece of 100 percent cotton cloth with a 200 thread count is secured to the frame with clamps. A piece of clear plastic, large enough to completely cover the cloth, is then placed completely over the cloth and also secured with the clamps. The frame assembly is placed in the plot with the cloth sampling media in contact with the turf. The frame is secured in place with spikes in each of the four corners of the frame to keep it from moving during sampling. The roller is placed just inside of the frame. Using the frame as a guide, the roller is pushed to the far end of the frame and pulled to the original starting point a total of five times. No downward pressure is exerted on the roller itself. The roller and frame are removed. Visible debris such as grass, thatch, granules, etc. are removed from the cloth sheet because this technique is designed to measure chemical residue which transfers to the cloth, not residue that adheres to particulate matter. The cloth is analyzed for chemical residue and the plastic is discarded. The roller and frame are reusable, provided they are decontaminated between sampling events.

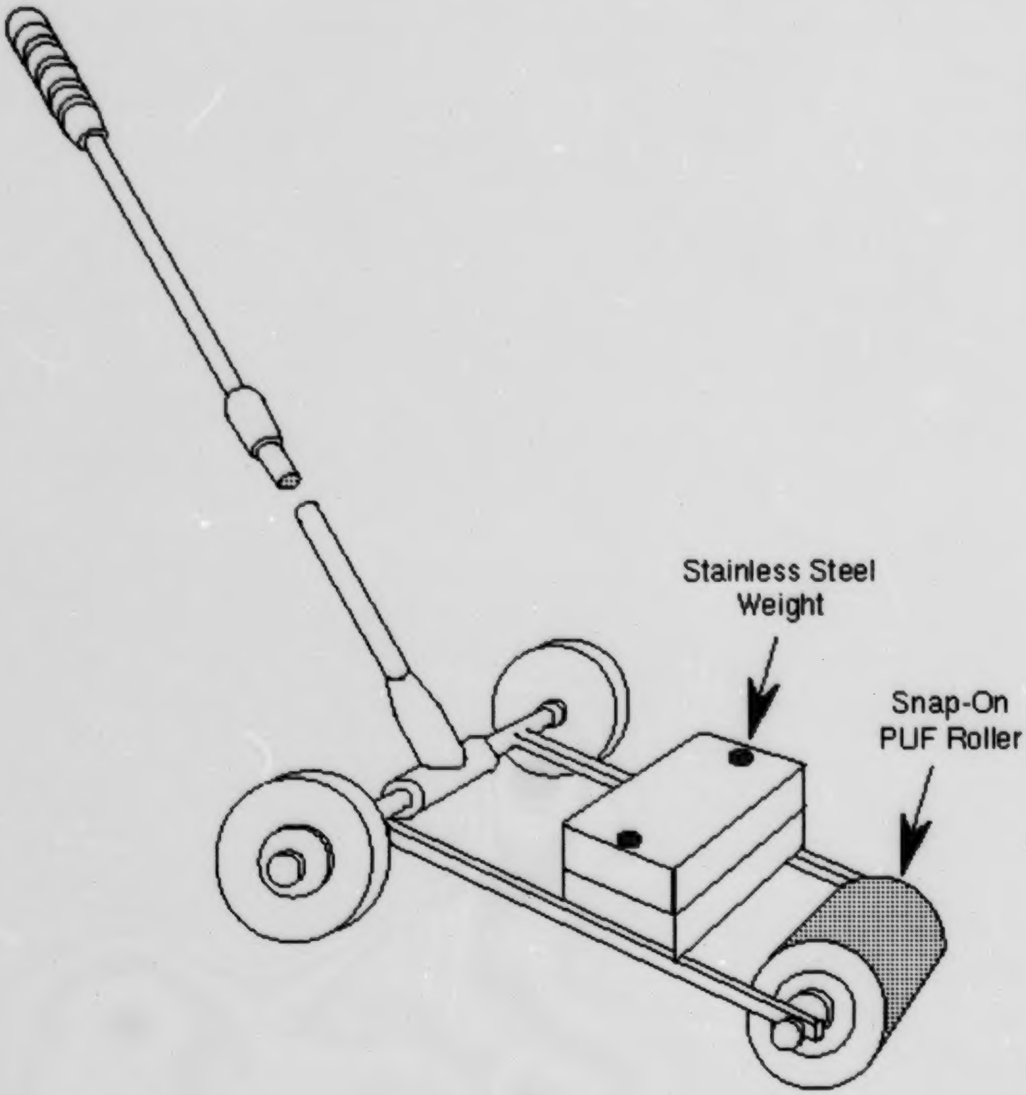
Stainless Steel
Weight
Snap-On
PUF Roller

Figure B4-1. PUF Roller Sampling Instrument

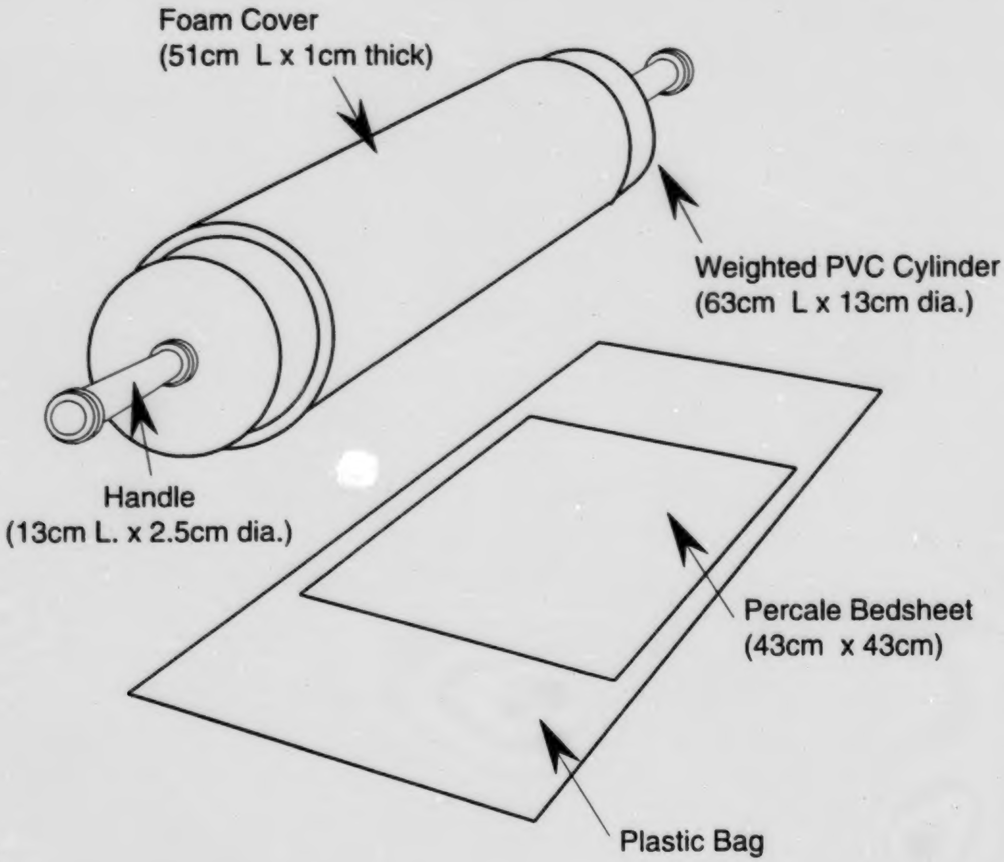
Foam Cover
(51cm L x 1cm thick)
Weighted PVC Cylinder
(63cm L x 13cm dia.)
Handle
(13cm L. x 2.5cm dia.)
Percale Bedsheet
(43cm x 43cm)
Plastic Bag

Figure B4-2. California Cloth Roller Sampling Device

4.2.5.5 *Drag Sled*

As with the two roller techniques, the drag sled method (also called the Dow sled) was originally designed for sampling indoor surfaces (U.S. EPA, 1994). (See Figure B4-3.) However, it has also found application in outdoor grassy areas (U.S. EPA, 1994; Vaccaro et al., 1993). This technique consists of dragging a weighted plywood block through a fixed area of treated turf. The block is 9 in^2 (3" x 3") in area and contains a removable denim pad attached to the underneath side. The weight placed on the block (usually a lead ball) can be varied, but the original testing (as with the roller techniques) has focused on the pressure exerted by a crawling or standing child. After sampling, the denim pad is removed and transported, on ice, to the laboratory for extraction and analysis.

4.2.6 General Considerations for Field Sample Collection

Control or background samples should be collected from the test plot prior to application of the test substance. Sufficient control samples should be collected so that fortified controls can be prepared on each sampling day. These fortified controls should be packaged, transported, stored, and analyzed concurrent with the dislodgeable residue samples. Please see Part C for detailed considerations on Quality Assurance and Quality Control recommendations.

4.3 SAMPLE STORAGE

Lawn surface residue samples and extracts should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis; more detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. The stability of other residues collected on sampling materials (i.e., cheese cloth, denim) should be determined and extractions of them should be conducted within their holding time limitations. The study investigator is responsible for demonstrating the stability of the samples under the storage duration and conditions used.

4.4 SAMPLE ANALYSIS

Pesticide residues should be dislodged from grass clippings within 4 hours of sample collection. Other transferable method samples should be stored appropriately until analysis. Validated methods of appropriate or sufficient sensitivity are needed for all sample analyses. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

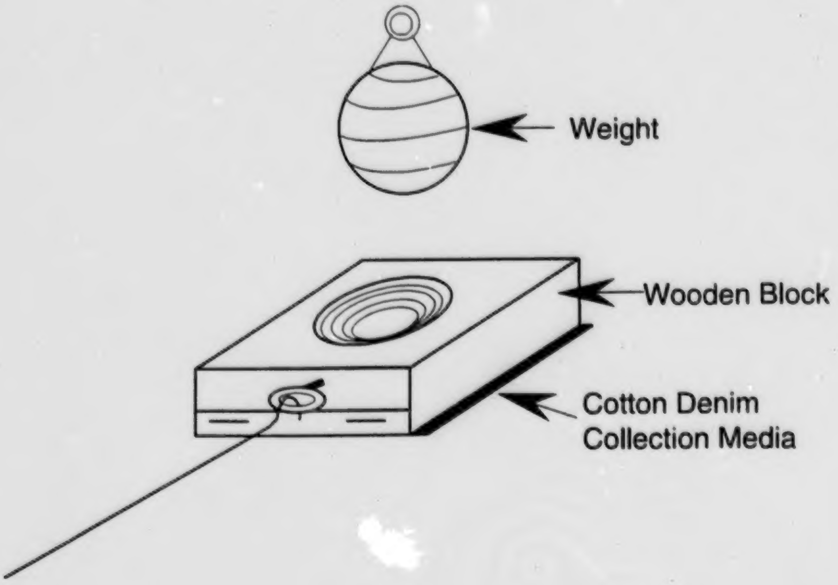
Weight
Wooden Block
Cotton Denim Collection Media

Figure B4-3. Dow Drag Sled Sampling Device

4.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates, exposure, and risk.

4.6 DATA PRESENTATION

Lawn surface residues from studies using the dislodgeable foliar residue and transferable residue techniques should be expressed as the amount of pesticide per leaf surface area, and as the amount of pesticide per area of lawn sampled as appropriate (i.e., leaf surface area is only for dislodging approach). For the other techniques described in this chapter (i.e., wipe, roller, and drag sleds), results should be reported as mg or μg of pesticide active ingredient per m^2 or cm^2 of lawn sampled. These data should be reported in tabular form for each sampling day. In addition, the best fit dissipation curve should be plotted (typically log-linear) with lawn surface residues on the Y-axis and time on the X-axis. Also, if the dislodgeable residue technique is used, the weights of various surface areas of grass clippings should be reported in tabular form followed by the regression analysis conducted to establish the surface area to weight correlation. Distributional data should be provided, to the extent possible.

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PART B - CHAPTER 5

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PART B - CHAPTER 5
SOIL RESIDUE DISSIPATION
GUIDELINE 875.2200

5.1 INTRODUCTION

This Guideline provides a description of the techniques and sampling strategies commonly used to characterize soil residue dissipation (SRD). Soil-borne residues, for purposes of this Guideline, represent total (not dislodgeable) chemical residues that are found in both surface and subsurface soils. Surface soil residues are of primary concern because contact with surface soils is usually more common than with subsurface soils. However, contact with subsurface soil may also be a concern for certain reentry activities such as potato harvesting, and where a mechanical apparatus is used. For the purpose of this guideline, surface soils are considered as those soil particles in the top 1 cm thick layer of soil. Subsurface soils are considered as anything below the surface layer of soil. SRD data may be used in conjunction with concurrent human exposure data to establish chemical transfer coefficients which are then used to determine restricted-entry intervals in occupational settings and exposures in residential scenarios. As an alternative, SRD data have been used in conjunction with dermal adherence data to estimate potential human exposures (U.S. EPA, 1988). Kissel et al. (1996a) have developed dermal adherence values for various human activities.

5.2 SAMPLE COLLECTION

5.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

5.2.2 Timing of Application

Sample collection should be conducted during the intended use season or under climatic conditions that are essentially identical to those encountered during the intended use season. Weather forecasts should be studied to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. For further information on climatological considerations, see Part B, Chapter 2 - Study Design.

5.2.3 Pesticide Application Rate and Frequency

Generally, the end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate, if possible. For example, typical rates are often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will also provide additional information about the relationship between the application and deposition rates. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, testing at a longer time interval between applications may prove to be beneficial if unacceptable risks may result. Registrants should note, however, that if the maximum rates or minimum application intervals are not monitored, subsequent label changes may be necessary. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance should be used.

5.2.4 Sampling Parameters

The following paragraphs provide a description of: where geographically sampling should occur; how long the dissipation must be characterized (i.e., the sampling period); the times within the sampling period that samples should be taken (i.e., sampling intervals); and the number of samples that should be taken at each sampling interval along with a description of where at the sampling location to sample.

5.2.4.1 *Number of Geographic Locations*

SRD samples are typically collected from at least three geographically distinct locations. This is usually necessary to ensure that varying climatic conditions, crops, and pest types are represented. Sampling locations should be selected based on the chemical use patterns, activities associated with the chemical use, and soil characterization data for selected locations. (See Chapter 2, Study Design, for more guidance.)

5.2.4.2 *Sampling Period*

Data should be collected in a manner that characterizes the dissipation mechanisms for the compound (e.g., three half-lives). Further, the sampling period should be reflective of the exposure conditions and toxicological endpoint of concern (i.e., acute or chronic). Typically, SRD dissipation rates are characterized for at least 35 days postapplication unless the compound has been found to fully dissipate in less than this time period. EPA has observed that this sampling period is adequate for characterizing pesticide dissipation under most use conditions; for most pesticides, significant dissipation occurs within the first week of application. Please note, however, that for more persistent pesticides a longer sampling period may need to be used.

5.2.4.3 *Sampling Intervals*

Generally, the length of time between sampling days should be relatively short in the beginning and should lengthen as the study progresses. EPA recommends that samples be collected prior to application on the day of application; on the application day at various hourly intervals after application (e.g., 4 hours and 12 hours may be appropriate); and on various days postapplication. For example, sampling on days 1, 2, 4, 7, 10, 14, 21, 28, and 35 after application may be appropriate. Please note that for certain pesticides (e.g., one that degrades quickly) shorter sampling intervals may suffice. However, the sampling should continue for 35 days, but all of the samples may not need to be analyzed if the pesticide has fully dissipated (i.e., nondetects for two sampling intervals). On the other hand, sampling may need to be continued beyond 35 days for more persistent pesticides. Special consideration should also be given to pesticides that exhibit biphasic dissipation kinetics.

If typical chemical use patterns involve a sequential series of treatments (i.e., multiple applications), samples in addition to the ones indicated above should be collected. Generally for multiapplication scenarios, the Agency recommends that samples be collected prior to and after each application on the day of application. Additionally, for all but the final applications (see above), samples should be collected at least every 7 days after each application during the intervals between application events (e.g., if multiple applications occur on a 14 day interval, then samples should be collected prior to and after each application and 7 days after each application). However, modifications to this sampling scheme may be proposed to the Agency if the market and use pattern will accept that reentry is prohibited between applications, or if the registrant is willing to accept the results and restrictions imposed by the alternative sampling scheme.

The proposed sampling intervals should be presented to EPA for review in the study protocol prior to the initiation of the study to ensure that they are agreeable to the Agency.

5.2.4.4 *Number of Samples and Sampling Positions*

The Agency recommends that at least three replicate samples be collected at each sampling interval. Each replicate sample should be taken from designated, distinct areas within the treated location. Samples should be collected in the worker contact zone (i.e., in those areas where workers will be conducting their activities). A sufficient number of subsamples must be collected and composited from each designated sampling location to generate samples that are sufficient for analysis. Exact sample collection procedures must be documented in any submission to the Agency. Control plots should also be established. Sufficient control samples should be collected to ensure that the same bulk sample can be used as a negative control matrix throughout all sample analyses. Additionally, samples from the control plots should be collected at each interval for assessment of the field sample collection and storage procedures.

Several approaches have been utilized by investigators to determine where to sample within treated sites. These include, but are not limited to: nondirected sampling and the planned approach for row crops. In nondirected sampling, field technicians enter a treated area and sample selected areas within the treated location at random. In the planned approach, investigators develop a scheme that predetermines sample collection locations. (See Figure B5-1.) EPA recommends that a planned approach be used for SRD sample collection.

5.2.5 Technique Validation

Validation of the soil sampling method is not required. Soils are to be analyzed for total residue levels contained in the sample. Validation of the analytical method used to evaluate chemical residues contained in soil is required, based on the guidance provided in Part C, Quality Assurance/Quality Control.

5.2.6 Sampling Techniques

Two sampling techniques are available for the conduct of a soil residue dissipation study. The first technique is surface soil sampling where the top layer of the soil (i.e., 1 cm thick) is removed and retained for analysis. The second technique is soil core sampling where samples are collected in 6-inch layers to depths that represent the exposure activity of concern. For most human activity patterns that are of concern, surface soil sampling is the recommended technique. However, there are activities such as potato harvesting and nursery stock transplanting where significant exposure to soils below the surface layer can occur.

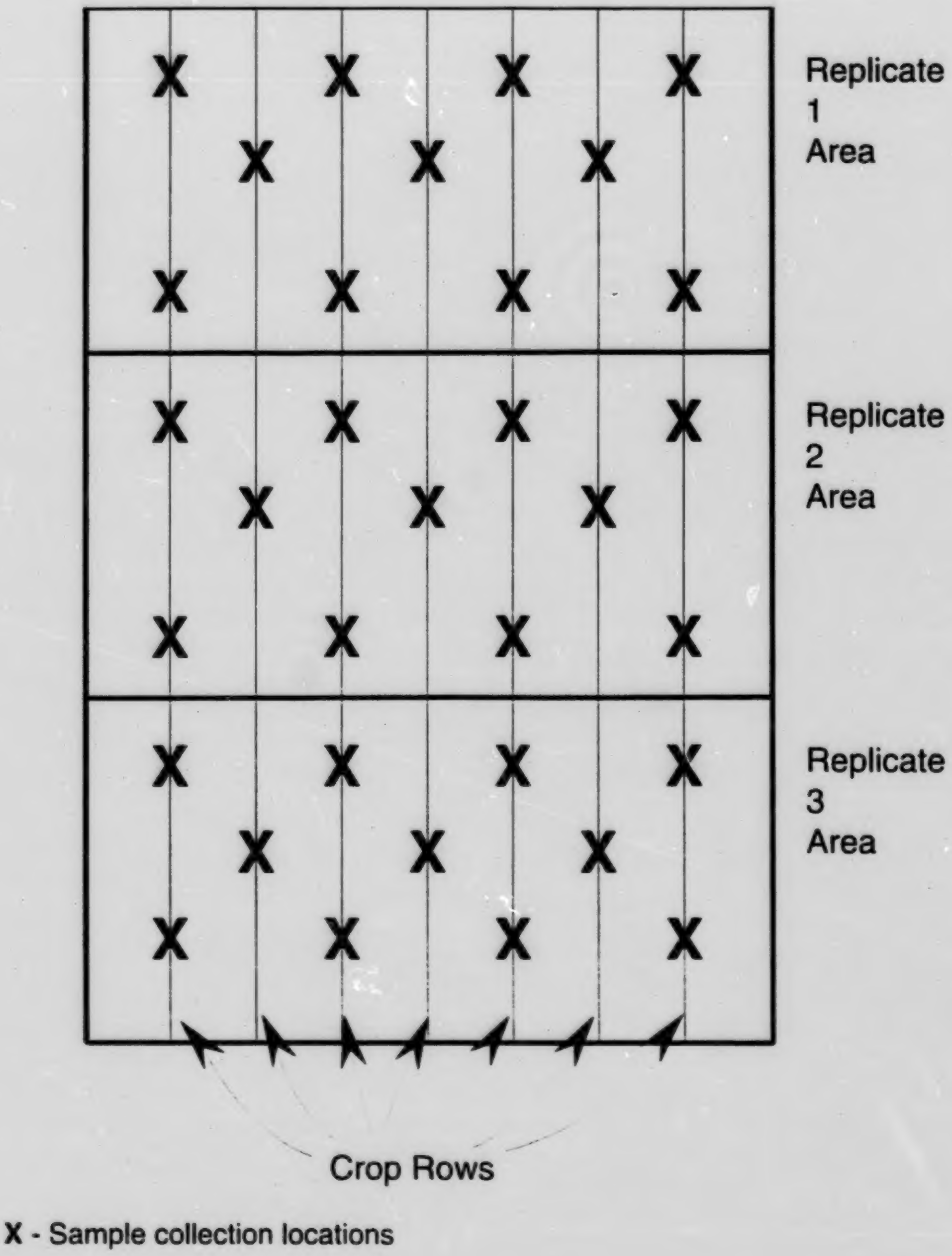
Replicate 1 Area
Replicate 2 Area
Replicate 3 Area
Crop Rows
X - Sample collection locations

Figure B5-1. Planned Approach for Field Crop Sampling

Surface soil samples may be collected using common equipment such as scoops, scrapers, and shovels. A template of known surface area (e.g., 1 foot by 1 foot) should be placed over the sampling area and the entire surface layer within the template should be removed as a replicate sample. The purpose of the template is to provide data that can be used to normalize residue levels based on the surface area sampled as well as on a weight basis. In cases where the treated plot has been tilled into furrows, samples should be collected from the top area of the furrow as this field arrangement is typically used for irrigation purposes and contact with the irrigation water may impact the dissipation of the analyte of interest.

If other surface soil sampling techniques are used, the sampling equipment must be thoroughly described in submissions to the Agency. Alternative types of techniques include: sweeping soil surface dusts (Berck et al., 1981); excavation of soil from the upper soil layers using templates (Zweig et al., 1985); and vacuuming soil dusts (Spencer et al., 1977).

Soil core samples may be collected using common techniques such as hand probes and mechanical soil coring machines. Both techniques are based on the principle of driving a cylinder into the ground, withdrawing the cylinder, and retaining the column of soil contained therein for analysis. Investigators are cautioned to use zero contamination devices wherever possible, particularly when sampling over several 6-inch depth levels. Zero contamination devices are double cylinder systems in which the outer cylinder is the soil core sampler and the inner tube is a clean cylinder (i.e., residue free sample container) that is driven into the ground concurrently and collects the sample. The inner cylinder prevents contamination between layers by retaining the sampled soil column intact and by preventing particles from shaking off the soil column and falling to the lower layers. Generally, the soil samples are retained for analysis in the inner cylinder. A number of subsamples should be collected to ensure that a sufficient quantity of soil is obtained for analysis at each sampled 6-inch layer.

5.2.7 General Considerations for Field Sample Collection

Control or background samples should be collected from the test plot prior to application of the test substance. Sufficient control samples should be collected so that fortified controls can be prepared on each sampling day. These fortified controls should be packaged, transported, stored, and analyzed concurrent with the dislodgeable residue samples. Please see Part C for detailed considerations on Quality Assurance and Quality Control recommendations.

5.2.8 Sample Preparation Procedures

Sample preparation procedures depend upon the objectives of the study. Based on the following data, investigators must consider soil conditions in the study design process and justify the soil sample preparation process. Dermal soil adherence data indicate that both particle size and percent moisture influence soil adherence to skin (Kissel et al., 1996b). Kissel et al. (1996b) used various soil types (i.e., loamy sand, two sandy loams, a silt loam, and sand) to evaluate factors that affect dermal adherence. Dermal soil adherence levels were determined using whole soils and soils at three size fractions (i.e., < 150 μm, 150 to 250 μm, and ≥ 250 μm to ≤ 425 μm). Percent moisture levels were also varied for each adherence test. Adherence of size- fractioned soils was evaluated at three percent moisture levels (i.e., <0.1 to 9, 10 to 19, and 21 to 27). Kissel et al. (1996) indicated that particles less than 150 μm are the primary contributors to soil adherence when the soil is dry (i.e., moisture is less than 2 percent). In contrast, particles greater than 250 μm are the primary contributors to soil adherence when soil is wet (i.e., percent moisture is between 12 and 18). Based on the whole soil test results, soil adherence increases as the percent moisture levels increase (e.g., 21 to 27 percent moisture soil adherence was generally an order of magnitude greater than adherence levels at percent moistures <2 percent). Generally, the Agency recommends that if moisture levels are ≤ 10 percent, then soils should be prepared for analysis by sieving to obtain a sample for analysis that contains all particles ≤ 250 μm. Conversely, if moisture levels are > 10 percent, then soils should be prepared by sieving to obtain a sample for analysis that contains all particles ≤ 425 μm. Typically, whole soil samples should never be submitted for analysis as these samples may contain coarse materials that would not likely adhere to skin but may contribute to a measured residue level (e.g., twigs and small stones).

The Agency prefers that common, mesh screen sieves be used to separate fine soil particles from more coarse soil components (Figure B5-2). Soil samples may be sieved using one of two approaches. The first approach requires that investigators sieve soil samples immediately after collection prior to freezing, storage, and analysis. The second approach involves freezing whole soil surface samples after collection and preparing those samples prior to analysis. Samples should be sieved while they are malleable, yet still partially frozen to ensure that there is no chemical residue loss (e.g., volatilization, soil metabolism, etc.). Aliquots of the fine soil components should be retained for three types of analysis: determination of chemical residues; soil characterization purposes; and determination of the percent water in each sample.

5.2.9 Soil Characterization

Investigators must characterize whole soil samples from each site used in the study (i.e., samples that have not been sieved) and samples that have been prepared for analysis. The Agency requires that

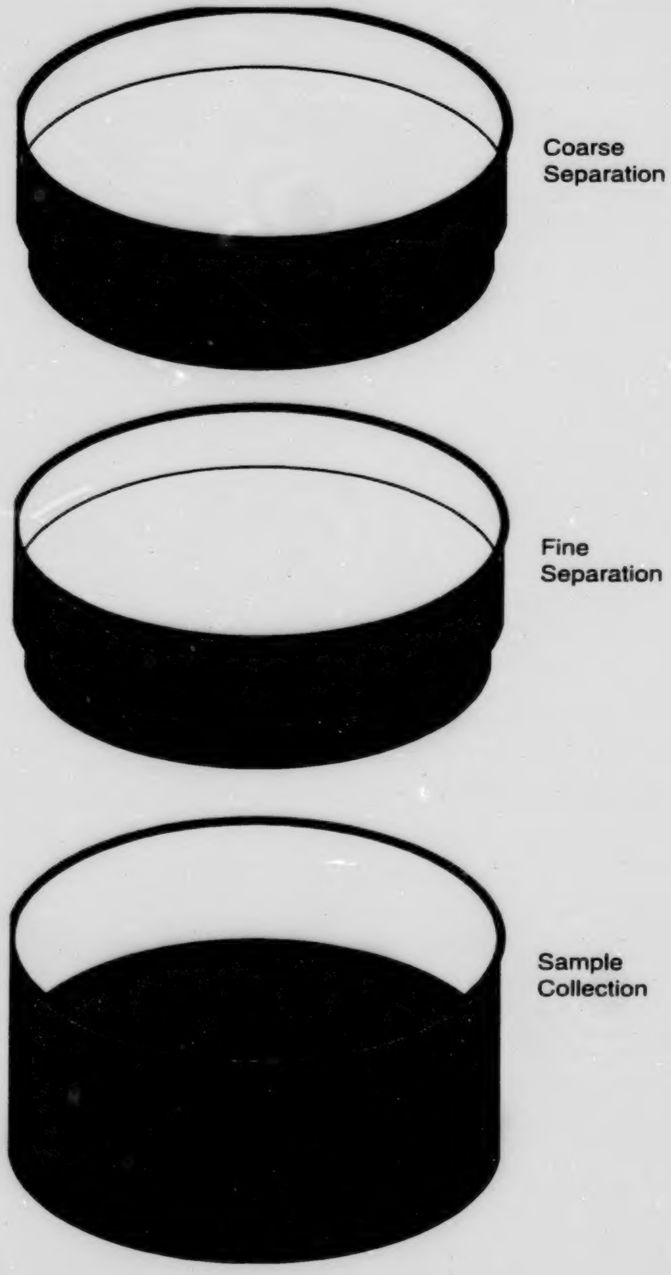
Coarse Separation
Fine Separation
Sample Collection

Figure B5-2. Soil Sieve/Screen Schematic

characterization be completed with at least triplicate samples collected from each study site. Soil characterization testing is a required element of all surface soil residue dissipation studies. Characterization of soils is based on the soil texture triangle illustrated in Figure B5-3 (U.S. EPA, 1991). Soil characterization data are required to ensure that the site selection process was adequate. Additionally, these data may provide useful information when attempting to evaluate soil residue dissipation kinetics especially when compared to any existing environmental fate data for the pesticide.

5.2.10 Water Content

In addition to the soil characterization requirements described above, the percentage of water contained in each soil sample intended for chemical residue analysis must be determined. Two gravimetric methods are available for determining the percentage of water in a soil sample. The first method involves preparing an aliquot of wet soil, placing the aliquot in a drying oven, and, after a predetermined time interval, removing the aliquot from the oven and weighing it to gauge water loss. The second method involves the use of a percent moisture meter (Figure B5-4). The device typically contains a high intensity visible light source (e.g., heat lamp), an analytical balance, and a timer for the light source (USGS, 1977). Other direct and indirect methods are available to determine the percent water in soil including alcohol burning, neutron scattering, and gamma-ray attenuation (USGS, 1977).

5.3 SAMPLE STORAGE

Soil residue samples and extracts should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis; more detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. The study investigator is responsible for demonstrating storage stability.

5.4 SAMPLE ANALYSIS

Validated methods of appropriate or sufficient sensitivity are needed for all sample analyses. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

5.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates, exposure, and risk.

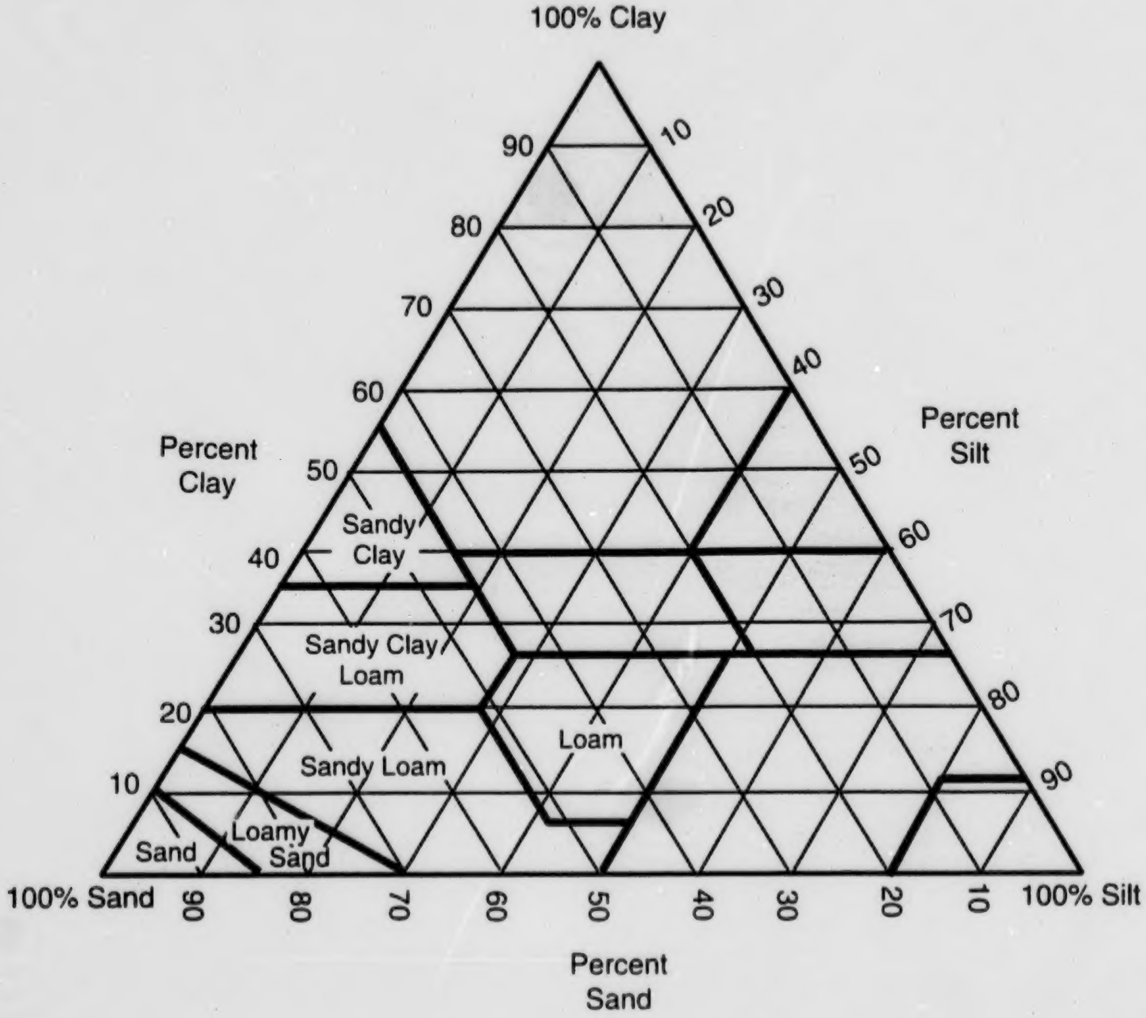
100% Clay
Percent Clay
Percent Silt
Percent Sand
100% Sand
100% Silt
90
80
70
60
50
40
30
20
10
Sandy Clay
Sandy Clay Loam
Sandy Loam
Loamy Sand
Sand
Loam

Figure B5-3. Soil Texture Triangle

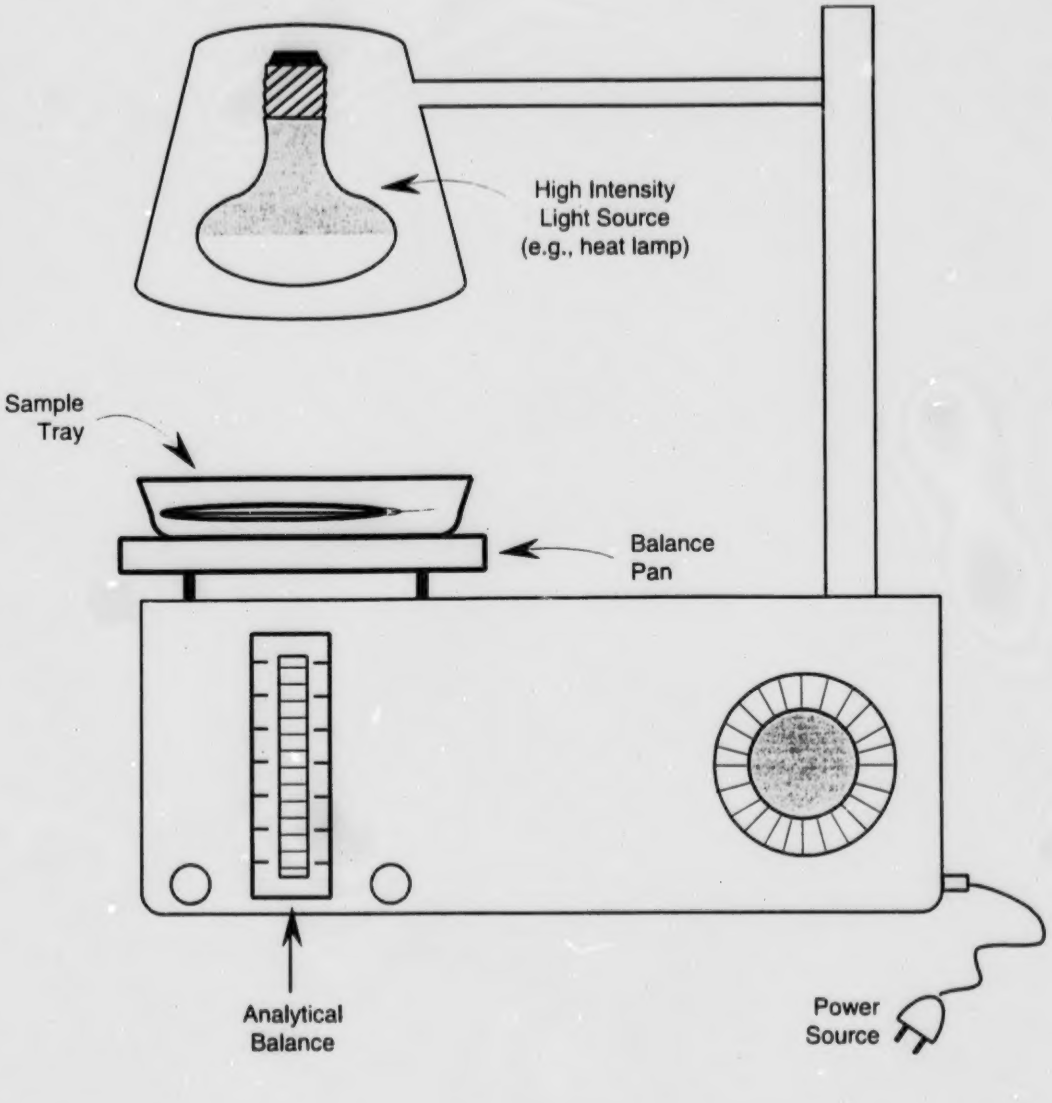
High Intensity
Light Source
(e.g., heat lamp)
Sample
Tray
Balance
Pan
Analytical
Balance
Power
Source

Figure B5-4. Percent Moisture Meter

5.6 DATA PRESENTATION

Soil residues should be reported as mg or μg of pesticide active ingredient on a per weight sampled and on a unit area sampled basis as appropriate (i.e., unit area for soil cores represents depth and diameter). These data should be reported in tabular form for each sampling day. In addition, the best fit dissipation curve should be plotted (typically log-linear) with soil residues on the Y-axis and time on the X-axis. Distributional data should be provided, to the extent possible.

REFERENCES FOR PART B, CHAPTER 5

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PART B - CHAPTER 6
INDOOR SURFACE RESIDUE DISSIPATION
GUIDELINE 875.2300

6.1 INTRODUCTION

This Guideline provides a description of the techniques and sampling strategies commonly used to characterize pesticide residues and dissipation on indoor surfaces. Such data are needed to quantify the transfer of dislodgeable residues from indoor surfaces to the skin. This information is used to determine whether or not a given pesticide may be used without appreciable risk in a residential setting.

The scope of the indoor environment encompasses a variety of settings in which human activities or properties are threatened by pests such as insects, microbes, rodents, fungi, or weeds. Examples of such areas where pest control is of interest are homes and apartments, greenhouses, farm buildings, health care facilities, schools and day care centers, and restaurants and food preparation establishments. Treated areas typically include the floors, carpets, furniture upholstery, cabinets, counter tops etc. of areas such as offices, kitchens, living rooms, and bedrooms.

Indoor surface residues may be generated from a variety of pesticide uses such as foggers, broadcast spray applications, crack and crevice treatments, vapor strips, moth repellents, residual termiticides, pet products, disinfectants, and indoor plant applications. According to the National Research Council (1993), the active ingredients found in most household products are cholinesterase-inhibiting compounds (i.e., organophosphates or carbamates). These chemicals can produce effects such as drooling and frequent urination, which may not be easily recognizable as resulting from pesticide intoxication because they resemble common behavioral patterns in children (Berteau et al., 1989). Other concerns include exposures to preservatives used indoors, such as those used to treat wood and those used in paint products. Outdoor-applied pesticides may also be tracked indoors where they become a secondary source of exposure (Nishioka et al., 1996). Also, persons who come into contact with pesticides as a result of their occupation may transport residues into their home (i.e., work clothing washed with other clothing, children touching contaminated clothing, etc.) Although EPA is cognizant of the existence of secondary exposure sources and the fact that humans, especially infants and children, are subject to these secondary sources, it recognizes that it is difficult to quantify these exposures due to limited data. Nevertheless, these secondary sources should not be overlooked when evaluating total human exposure.

Exposure to pesticides used in and around indoor and residential settings may occur via multiple routes of exposure -- dermal, inhalation, or nondietary ingestion. Dermal postapplication exposure results when the skin contacts contaminated dust or surfaces, such as carpets, vinyl tile flooring, counter tops, upholstery, etc. (See Part B, Chapter 7 - Dermal Exposure.) Humans may be exposed to dust, vapors, and aerosols via the inhalation route. (See Part B, Chapter 8 - Inhalation Exposure Monitoring for techniques used to assess inhalation exposure, including indoor exposure.) Oral exposure (nondietary ingestion) may result from hand-to-mouth or object-to-mouth activity (especially for children), or through the consumption of contaminated food (including contamination while preparing, serving, and eating meals and snacks), and ingestion of dust or soil. (See Part B, Chapter 9 for information on non-dietary exposure assessment techniques.)

The techniques described in this chapter to measure indoor surface residues or dust residues may be used with the methods provided in Part B, Chapter 7 for dermal monitoring to estimate transfer of residues to human skin or with guidance provided in Part B, Chapter 9 - Nondietary Ingestion Exposure Assessment to estimate exposures from hand to mouth transfer.

The measurement of indoor pesticide residues is particularly important for populations that may spend a large portion of their time in indoor settings (i.e., children). Due to pesticide poisoning incidents involving children and the significant differences in the potential for pesticide exposures between adults and children, it may be necessary to focus specific attention on the assessment of pesticide exposures to children. The exposure potential for children (inclusive of infants and toddlers) may be greater than for adults because of several physiological, behavioral, and metabolic factors. The following are some examples:

- Children have a higher surface area to body weight ratio than adults.
- Although the inhalation rate in children is less than in adults, the volume inhaled on a body weight basis is greater in children.
- Children spend a significant amount of time crawling, playing or lying on the floor; consequently, pesticides may be absorbed by exposed skin if the contacted surface is contaminated.
- Children have increased mouthing activity and a lesser awareness of hygiene (i.e., eating food that has been dropped onto the floor, not washing hands after playing in dirt/soil), and as a result, it has been estimated that the risk of exposure to indoor and outdoor contaminants in soil and dust may be up to 12 times higher for children than adults (Hawley, 1985).
- The breathing zone for children is usually closer to the floor than adults.
- Infants may wear less clothing than adults while at home, i.e., wearing a diaper while crawling on the carpet, resulting in a greater surface area for potential exposure.
- Children, particularly infants, spend more time in the home than adults.

These factors along with other metabolic parameters and the stages of growth and development may make children more susceptible to passive indoor and residential exposures.

Recently, EPA has been conducting research aimed at developing methods for determining the concentrations of chemical substances on surfaces and in materials that are transferred to the skin or become available on the surface of the skin for possible dermal absorption and ingestion through hand-to-mouth activity (U.S. EPA, 1997a). The objectives of the research are to: (1) compare methods (i.e., wipe test, coupons, and dislodgeable residue) to determine the dissipation of malathion residues from residential media (carpet, vinyl flooring, and painted sheetrock); (2) measure the dissipation of residues of malathion and the production and dissipation of malaoxon under different conditions of humidity and temperature; and (3) determine the transfer of residues of malathion from the residential surfaces to human skin, cadaver skin, artificial skin, porcine skin, and passive dosimeter materials. The transferability of residues of malathion and malaoxon to human skin *in vivo* was compared to the transferability on human cadaver skin *in situ* and other skin substitutes. Transferability ratios were determined for the model skin surrogates. The results of this research are expected to assist in reducing the uncertainty associated with the relationships between pesticide residues in residential environments and the transfer of residues to the skin (U.S. EPA, 1997a).

6.2 SAMPLE COLLECTION

6.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

6.2.2 Timing of Application

Studies should be conducted under ambient conditions similar to those encountered during the intended use season or the season with the most frequent anticipated use. Ambient conditions (i.e., temperature, relative humidity, barometric pressure, ventilation, etc.) should be monitored throughout the study. Ventilation, among other factors, affects the accumulation, decay, transformation, transport (between rooms and media), and transferability (from media to body) of surface residues. Consequently, the time of application (e.g., summer versus winter) can impact the quantity of transferable indoor surface residues. For instance, studies have demonstrated that relatively nonpersistent insecticides will remain within structures protected from sunlight and ventilation for several weeks (Leidy et al., 1993).

6.2.3 Pesticide Application Rate and Frequency

Generally, the typical end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate, if possible. For example, typical rates are often used in cancer assessments (U.S. EPA, 1997b). Monitoring at more than one rate will provide additional information about the relationship between the application and deposition rates. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, the potential accumulation of residues from multiple applications should be considered.

Several methods are used in the application of indoor and residential pesticides. Some of the most common types of pesticides used indoors include: pesticide foggers such as flea bombs; spot or crack and crevice treatments; vapor strips for flying insects; broadcast spray applications; moth repellents; termiticides; pet products such as flea collars, dips and shampoos; disinfectants; and indoor plant applications. When several methods of application are available (e.g., fogger versus crack and crevice treatment), data should be provided in the protocol to support the rationale for selecting the application technique(s) monitored.

6.2.4 Sampling Parameters

Generally, indoor surface residue measurements should be collected over a sampling period that is sufficient to characterize residue dissipation. The following paragraphs provide a description of the locations where sampling should occur; how long the dissipation must be characterized (i.e., the sampling period); the times within the sampling period that samples should be taken (i.e., sampling intervals); and the number of samples that should be taken at each sampling interval along with a description of where at the sampling location to sample.

6.2.4.1 *Number of Locations*

It is recommended that indoor surface residue (ISR) samples be collected from several different types of the media of interest. For purposes of an ISR study, the media of interest may be carpeting, hard surface flooring, counter tops, or other materials. It is recommended that as many types of the media of interest be sampled as possible to account for the broad variability in construction materials used. For example, if the media of interest is carpeting, the investigator may wish to sample a range of carpet types that represent differences in quality, stain resistance, and material. To ensure that the selected sample types are acceptable to the Agency, a study protocol should be submitted to the Agency before sampling begins.

6.2.4.2 *Sampling Period*

Data should be collected in a manner that characterizes the dissipation mechanisms for the compound (e.g., three half-lives). Further, the sampling period should be reflective of the exposure conditions and toxicological endpoint of concern (i.e., acute or chronic). Typically, ISR dissipation rates are characterized for at least 72 hours postapplication unless the compound has been found to fully dissipate in less than this time period. EPA has found that this sampling period is adequate for characterizing pesticide dissipation under most use conditions; for most pesticides used in residential settings, significant dissipation occurs within the first 72 hours after application. Please note, however, that for more persistent pesticides a longer sampling period may need to be used. In addition, the recent passage of the Food Quality Protection Act may result in the need for monitoring over longer periods to allow for the aggregation of long-term exposures from multiple sources (i.e., dietary plus dermal). Registrants should present the proposed sampling period in the study protocol prior to initiation of the study to ensure that it is agreeable to the Agency.

6.2.4.3 *Sampling Intervals*

Generally, the length of time between sampling should be relatively short in the beginning and should lengthen as the study progresses. EPA recommends that samples be collected prior to application on the day of application and on the application day at various intervals after application. For example, sampling at 1, 4, 8, 12, 24, 48, and 72 hours after application may be appropriate. These sampling intervals are provided for illustrative purposes only. Please note that for certain pesticides (e.g., one that degrades quickly) shorter sampling intervals may suffice. However, the sampling should continue for at least 72 hours, but all of the samples may not need to be analyzed if the pesticide has fully dissipated (i.e., nondetects for two sampling intervals). On the other hand, sampling may need to continue beyond 72 hours for more persistent pesticides. U.S. EPA (1996) observed detectable levels of chlorpyriphos residue in plush carpet up to 43 days after application. Transfer of chlorpyriphos residues to sampling media decreased by an order of magnitude within the first month after application and by two orders of magnitude after three months. Special consideration should also be given to pesticides that exhibit biphasic dissipation kinetics. The data for the pesticide of interest should be collected for each of the selected surface media. The dissipation of the pesticide would be expected to be dependent on the types of surface media and the environmental conditions associated with its use.

The proposed sampling intervals should be presented to EPA for review in the study protocol prior to the initiation of the study to ensure that they are agreeable to the Agency.

6.2.4.4 *Number of Samples and Sampling Positions*

The number of samples and the sampling positions depends on the methodology selected (e.g., polyurethane foam roller). However, as a general rule, three samples per surface type per time period (i.e., triplicate samples) are recommended. The sampled areas should be marked so that they are not subsequently over-sampled. Frequently, a tape, ruler, or template is used to indicate where samples have been taken. Control plots should also be established. Sufficient control samples should be collected to ensure that the same bulk sample can be used as a negative control matrix throughout all sample analyses. Additionally, samples from the control plots should be collected at each interval for assessment of the field sample collection and storage procedures.

The areas chosen (e.g., rooms, hallways, etc.) should be representative of those typically treated with a pesticide and the environmental conditions expected in the intended use area. Variability in the surface types (e.g., stain-resistant carpet, hardwood flooring), surface conditions (e.g., old or worn vs. new), ventilation and air filtration, room size, etc. should also be considered.

6.2.5 Sampling Techniques

Several methodologies of assessing exposures to pesticides used indoors and around residential settings have been developed. Some of these techniques are used for measuring transferable surface residues from floors (e.g., Polyurethane Foam Roller, California Cloth Roller, and Dow Drag Sled) or other indoor surfaces (i.e., Lioy-Weisel-Wainman Sampler, Wipe Samples, and Hand Press). Others are used to sample bulk dust and debris (i.e., vacuum cleaners), or total residues (i.e., coupons). These guidelines will provide an overview of the current methodologies of measuring indoor pesticide total or transferable residues, as expressed in the published literature. Research is relatively new and is continuing in the area of indoor/residential exposure monitoring, and any guidance provided herein should be considered interim. Due to the lack of sufficient data to adequately endorse a specific sampling technique, EPA will not require the performance of exposure studies using a specific technique, but a minimum acceptable criteria for conducting these studies will be provided. It will be at the discretion of the study investigator to select the methodology most suitable for measuring human exposure for the use(s) intended. In addition, the study investigator is encouraged to propose new methodologies to estimate human exposure and to validate existing methods. However, it should be noted that the selected technique must satisfy specific performance criteria as detailed in Part C, Quality Assurance/Quality Control.

The following list briefly describes some sampling methodologies currently described in the literature. For a more detailed explanation of the sampling methodologies, refer to "Methodologies for Assessing Residential Exposure to Pesticides" (U.S. EPA, 1994), and published literature. Recently, the efficiency of several of these methodologies (i.e., the polyurethane foam roller, California cloth roller, and Dow drag sled) for measuring dislodgeable residue transfer from floors (i.e., vinyl flooring and carpets) were compared (U.S. EPA, 1996). Information on the observed strengths and weaknesses associated with these methods, based on U.S. EPA (1996), are shown in Table 6-1. In addition, round-robin testing of several of these methods (i.e., the California cloth roller, the polyurethane foam roller, and the Dow drag sled) was performed to evaluate sampling precision (U.S. EPA , 1997c). The results indicated that reproducible and consistent data can be obtained using these methods (U.S. EPA, 1997c).

6.2.5.1 *Polyurethane Foam (PUF) Roller*

The polyurethane foam (PUF) roller sampler was designed to measure transferable residues from contaminated floor surfaces that a child may contact during various activities (i.e., crawling) (Lewis et al., 1994; Hsu et al., 1991). A dry PUF ring (8.9 cm outside diameter x 8 cm long) is secured on a 7.2 lb stainless steel roller. (See Figure B6-1.) The PUF ring is rolled over a surface once in both directions at the rate of 10 cm/second, exerting a pressure of 7,300 Pa, comparable to that of a toddler standing or crawling, (6,900 Pa - crawling and 8,600 Pa - standing). After the two rolls, the PUF roll cover is removed from the roller for analysis. The exposed rollers must be carefully handled to avoid contamination. Although it has been suggested that the PUF roller and other sampling devices be moistened with water to stimulate the moistness of the human skin, studies conducted by U.S. EPA (1996) indicate that the measurement variability increased substantially when moist contact media were used. According to U.S. EPA (1996), "the increased measurement variation with moistened media may be a serious impediment to the use of moistened media in field studies, since many more replicates would be required to detect a difference in transfer rates." Thus, the use of moistened media is not recommended unless first validated by the user for the specific pesticide formulation(s) under study. The EPA is continuing investigations to find a suitable moistening agent other than water. Nishioka et al.

Table 6-1. Observations from Field Use of Dislodgeable Residue Methods

Strengths	Weaknesses
Cloth Roller	
Simple in design Inexpensive to build from available materials	Sampling cloth tends to bind and shift from original position Plastic bag cover may adhere to PUF sleeve on roller from static Difficult to operate due to mass of roller Operator must contact treated surface Susceptible to added pressure from operator Transfer affected by roll orientation relative to lay of carpet fibers
Drag Sled	
Simple in design Inexpensive to build from available materials Simple to use	Drag contact unlike most skin contact with carpet Drag contact is potentially directional relative to lay of carpet
PUF Roller	
Consistent use across operators due to few variables Relatively simple to use Foam roller contact is more like skin contact	Expensive to build or purchase

Source: U.S. EPA (1996)

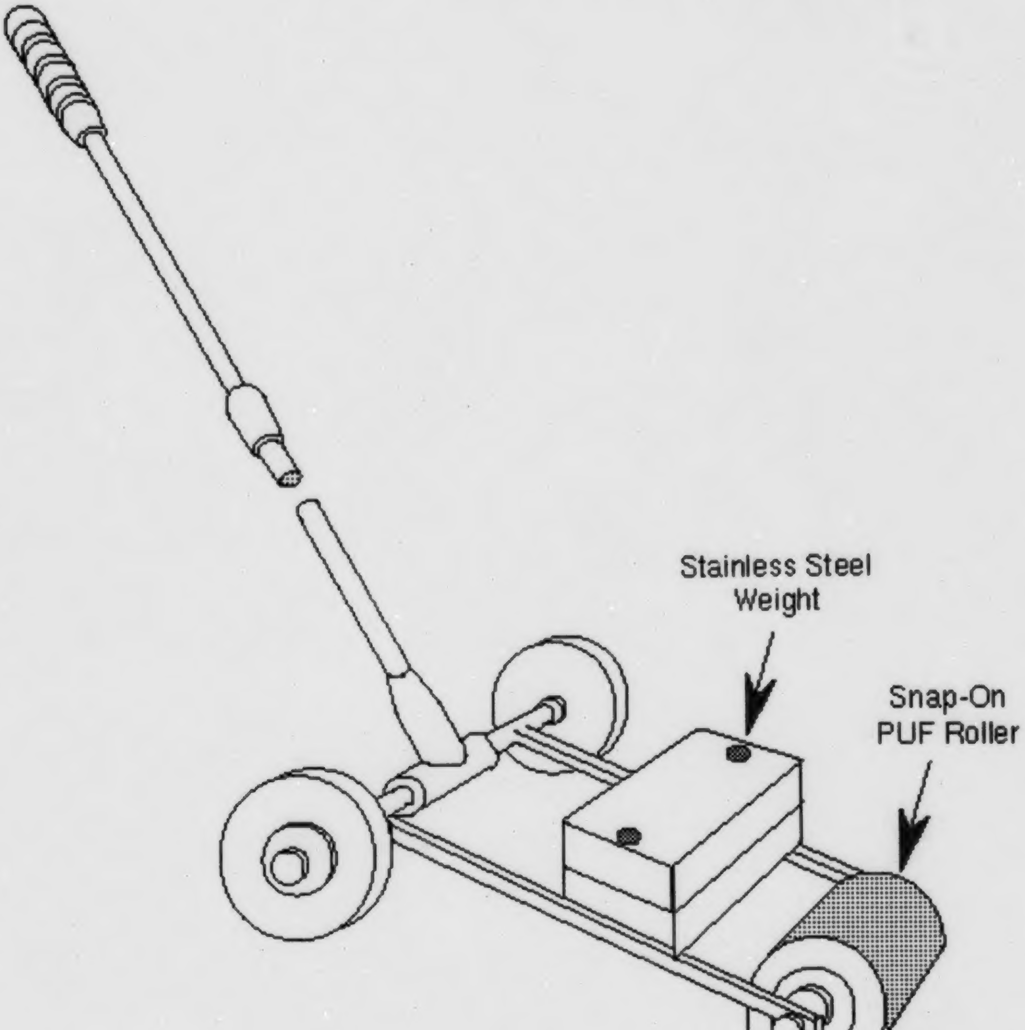
Stainless Steel
Weight
Snap-On
PUF Roller

Figure B6-1. PUF Roller Sampling Instrument

(1996) employed a "sweat simulator" composed of a buffered acetonitrile/water mixture to collect dislodgeable residues of several pesticides from carpet and turf.

6.2.5.2 *California Cloth Roller*

The California Cloth Roller technique is designed to collect transferable residues from floors. A percale cotton/polyester bedsheet is placed on the surface and covered with a sheet of plastic (or clean cotton toweling) (Ross et al., 1991). (See Figure B6-2.) A weighted foam covered roller (similar to a baker's rolling pin or paint roller) is rolled over the plastic bedsheet ten times backward and forward without additional pressure. After 10 passes, the percale cloth is collected, transported to the laboratory on ice, extracted, and analyzed. Recently, the Outdoor Residential Exposure Task Force (ORETF) developed a modification of the California Cloth Roller (Johnson, 1998). The roller is a 4-inch diameter by 24-inch long PVC pipe. The outside of the roller is wrapped with half-inch polyurethane foam sheet, or equivalent pipe insulation, for cushioning and traction. Enough weight is added to the inside of the roller to bring the total weight (excluding the handle) to 32 pounds, which is evenly distributed across the length of the roller. A handle is added to the roller. A rectangular-shaped frame is made of PVC material with inside dimensions of 24.5 x 36 inches. A 27 x 39 inch piece of 100 percent cotton cloth with a 200 thread count is secured to the frame with clamps. A piece of clear plastic, large enough to completely cover the cloth, is then placed completely over the cloth and also secured with the clamps. The frame assembly is placed in the plot with the cloth sampling media in contact with the turf. The frame is secured in place with spikes in each of the four corners of the frame to keep it from moving during sampling. The roller is placed just inside of the frame. Using the frame as a guide, the roller is pushed to the far end of the frame and pulled to the original starting point a total of five times. No downward pressure is exerted on the roller itself. The roller and frame are removed. Visible debris such as grass, thatch, granules, etc. are removed from the cloth sheet because this technique is designed to measure chemical residue which transfers to the cloth, not residue that adheres to particulate matter. The cloth is analyzed for chemical residue and the plastic is discarded. The roller and frame are reusable, provided they are decontaminated between sampling events. See Part B, Chapter 4 - Dislodgeable Foliar Residue Dissipation: Lawn and Turf, for more information. This modified method was developed for outdoor sites, but may also be suitable for use in indoor settings.

6.2.5.3 *Drag Samplers*

The Dow Drag Sled technique has been developed to estimate the transfer of pesticide from the contaminated floor surface to the skin (i.e., transferable residues) (Vaccaro et al., 1991). The technique consists of dragging a weighted (8 pound) 3 inch x 3 inch plywood block on which a removable denim

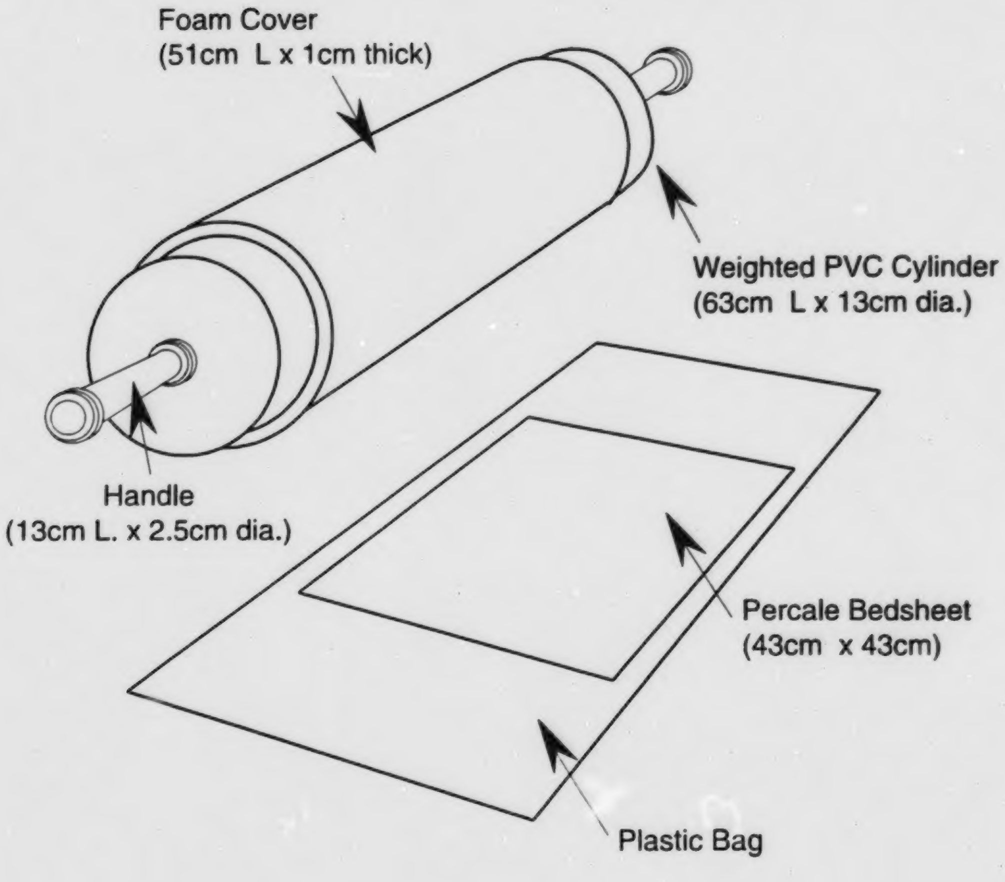
Foam Cover
(51cm L x 1cm thick)
Weighted PVC Cylinder
(63cm L x 13cm dia.)
Handle
(13cm L. x 2.5cm dia.)
Percale Bedsheet
(43cm x 43cm)
Plastic Bag

Figure B6-2. California Cloth Roller Sampling Device

patch is attached. (See Figure B6-3.) After dragging the sled once over a 3 inch x 4 foot carpet strip (sample area equal to 1-square foot) at 6-8 cm/second, the denim cloth is removed for analysis. The denim pad is removed after each drag.

Lioy et al. (1993) developed a similar device (i.e., the Lioy-Weisel-Wainman (LWW) Sampler) to sample flat surfaces. The sampler consists of two sections; one serves as a template and the other is a movable 4 cm square block that holds a filter sampling media that is moistened with "Type I reagent water." The template is placed on the sampling surface and the square block is dragged across the template opening, filter side down, a total of three times. Filters are then removed and analyzed for dust loading or the elemental content of sampled dust. Lioy et al. (1993) measured the reproducibility and dust (i.e., road dust and potting soil) collection efficiency of the LWW sampling device on three types of surfaces (i.e., painted shelving, formica, and wood paneling). For the purposes of these experiments, the filter media was polyethylene drain disc material that had been cut into rectangles. The results indicated "a high degree of reliability for flat surfaces." The authors noted, however, that porous surfaces may not be sampled as efficiently. Although Lioy et al. (1993) did not use the LWW sampler to sample for pesticides, the device may be suitable for measuring pesticides in surface dusts.

6.2.5.4 *Vacuum Cleaners*

Vacuum cleaners provide a method for collecting residues associated with dust and debris. In an effort to measure pesticides in house dusts, a potential reservoir or secondary source of exposure, a standard home vacuum cleaner has been used to collect samples from residential houses. In addition, a high volume surface sampler (HVS3) (Roberts et al., 1991a; Lewis et al., 1994) was designed to collect dust from carpets. HVS3 is a specially designed vacuum device with a stainless steel sampling train (Roberts et al., 1991b). (See Figure B6-4.) The device samples at a flow rate of 9.5 L/s (20 cfm) and passes the vacuumed dust through a cyclone that efficiently collects particles larger than 5 μm in a bottle at the base of the cyclone. A bulk sample of approximately 2 g of dust can be collected in up to 10 minutes. Studies employing a fine particle filter and PUF plug behind the cyclone have demonstrated greater than 99 percent of the vacuumed dust and 97 percent or more of tested pesticides (i.e., chlordane, aldrin, heptachlor, chlorpyrifos, and diazinon) are collected in the cyclone bottle (Roberts et al., 1991a; ASTM, 1996). Vacuum sampling devices are currently being used by EPA to collect dust samples for metals and pesticides analyses. It has also recently been used to collect carpet dust samples for pesticide analysis as part of the National Human Exposure Assessment Survey (NHEXAS) (Lebowitz et al., 1995). The HVS3 vacuum sampler has recently been used to collect carpet dust samples for pesticide analyses as part of the joint Agency (NCI, EPA, NIEHS) Agricultural Health Study (Camann et al., 1997). Concentrations of 32 pesticides in carpet dust from 9 farm households were evaluated.

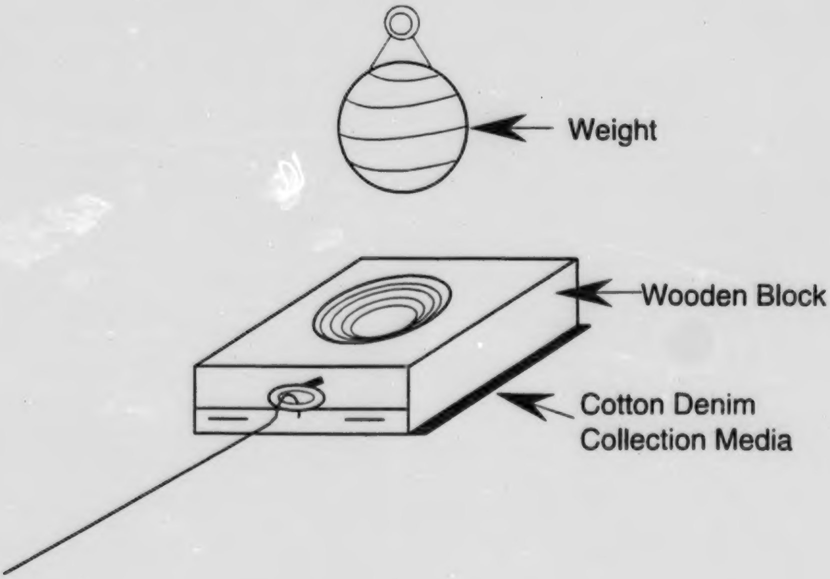
Weight
Wooden Block
Cotton Denim
Collection Media

Figure B6-3. Dow Drag Sled Sampling Device

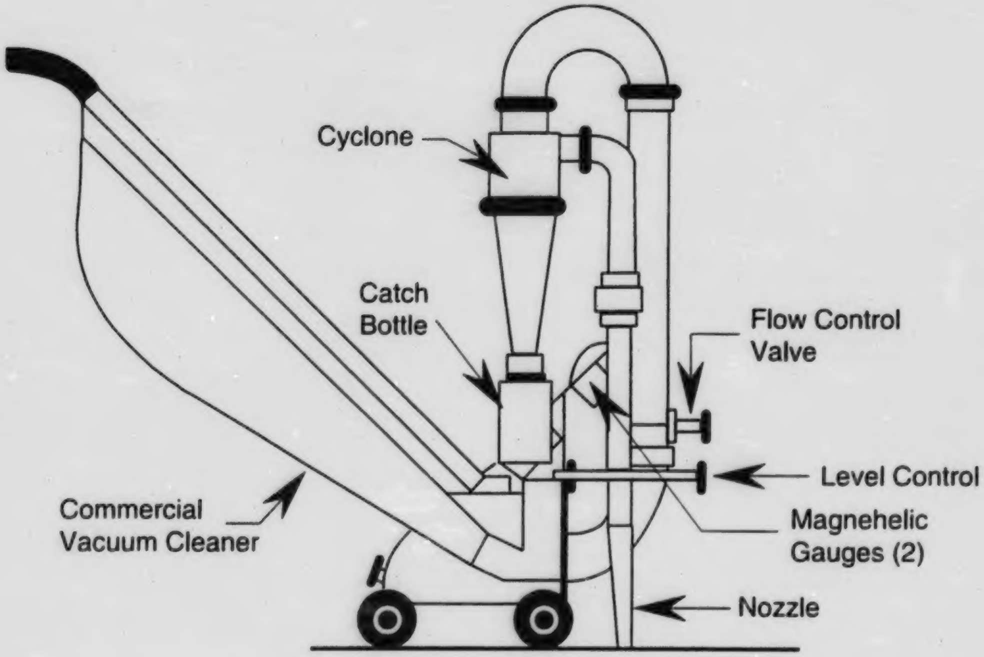
Cyclone
Catch Bottle
Flow Control Valve
Level Control
Magnehelic Gauges (2)
Commercial Vacuum Cleaner
Nozzle

Figure B6-4. HVS3 Sampling Device

6.2.5.5 *Coupons*

Coupons may be used to collect total or transferable residues. The "Gunther/Iwata" coupon approach is one method used for sampling the amount of total or transferable residues.

Typically, coupons are used to measure or confirm deposition rates (i.e., evaluation of the source strength). Deposition of pesticide residues may be measured using alpha cellulose or cotton gauze coupons placed in triplicate at indoor locations where deposition is likely to occur. The coupons are collected and residues are extracted with an appropriate solvent to measure total pesticide residues. Krieger et al. (1997) used 100 percent cotton dosimeters (i.e., T-shirt type material) to capture surface residues. The dosimeters were placed on aluminum foil to prevent penetration breakthrough, and positioned in locations on the floor where deposition was expected to occur. Under certain circumstances, it may also be appropriate to use the coupons consisting of the indoor material onto which the pesticide residues are deposited (i.e., textiles such as upholstery or carpet).

Coupons are also sometimes used to estimate dissipation rates. Coupons simulating materials commonly found in indoor settings (i.e., carpet, tile, hardwood, glass, etc.) are placed near or on the surfaces that they represent. It is essential that the coupon material used for such dissipation studies be representative of the indoor surface of interest. For example, carpet samples should not be used to represent hard surfaces. A sufficient number of coupons is placed at each location to provide triplicate samples for each sampling interval and field spikes. The coupons are collected at appropriate time intervals (i.e., before application, immediately after application, 2 hours, etc.), and an appropriate solvent is used to extract residues. Clean forceps should be used to pick up each coupon to prevent contamination between coupons.

6.2.5.6 *Wipe Samples*

Residues that can be transferred from the treated surface as a result of contact can be measured using wipe sampling. This technique uses moistened cotton gauze pads to sample a standardized area (e.g., 1-square foot). This is a relatively simple technique that can be conducted on a variety of surfaces. The number of times that the surface should be wiped is not consistent. A weight may be attached to the sampling pad to apply uniform pressure. Research has shown that when two wipes are done (sampled area wiped twice using two pads in two directions and applying maximum pressure by the hand), the second wipe can yield almost as much residue as the first wipe (Naffziger et al., 1985). To minimize variability in results, certain factors should be considered (standardizing the sampling material, standardizing the area to be wiped, outlining the boundaries of the surface to be wiped with tape or a template, wiping the sample area once with firm even pressure, collecting samples in triplicate, checking the moisture content of the wipe). As with the previous techniques, samples should be collected at sufficient intervals to establish a dissipation curve. In general, wipe samplers should only be used on hard surfaces (i.e., not carpeting).

6.2.5.7 *Hand Press*

The hand press is a sampling technique used to collect experimental data on transferable residues. It is typically used as an experimental research tool and not as a monitoring method. The hand press method is similar to the wipe sampling technique with the difference being the sampling medium (hands, with or without gloves, versus cotton gauze pads). Hsu et al. (1991) used the palm of the hand (excluding fingers) pressed at a pressure of approximately 1 lb/inch^2 sequentially over the designated testing area. This technique has also been used to validate the PUF roller technique (Hsu et al., 1991). In a technique developed by Lewis et al. (1994), the hand is first washed with soap and water and allowed to dry for 10 minutes. It is then pressed, palm-only, 10 times on a scale covered with cleaned aluminum foil to achieve a uniform pressure of 12 lbs. (5.4 kg, equivalent to 7,300 Pa), and then pressed, palm-only, 10 times sequentially on the carpet (or bare floor) along a 100 cm path using a 10 cm x 100 cm template.

6.2.5.8 *Migration Method*

Potential exposures to pesticides (e.g., antimicrobials) may occur as a result of residues that "leach" from treated articles (i.e., impregnated materials such as textiles or children's toys). Exposure to these residues may occur as a result of dermal contact or non-dietary contact (i.e., mouthing behavior). The U.S. Food and Drug Administration (FDA) recommends the use of a migration technique to assist petitioners in the preparation of the chemistry portion for indirect food additives (FDA, 1995). Indirect food additives are defined by FDA as "substances used in the processing, packaging, holding, and transporting of food that have no functional effect in the food but which may reasonably be expected to become components of food" (FDA, 1995). Although the Series 875, Group B Guidelines are not intended to address dietary exposures, this migration technique may have applicability in assessing migration of pesticides from impregnated materials to surfaces to which humans have non-dietary contact.

FDA (1995) recommends the use of a migration cell in which a material sample of known surface area is extracted by a known volume of solvent. FDA (1995) recommends that the surface area to solvent volume ratio should be reflective of the food and packaging materials of interest. The material sample is placed in the solvent so that the solvent flows freely around the material. "The headspace is gas-tight and liquid seals are maintained" (FDA, 1995). The cell is mildly agitated for 10 days or more at a temperature that is reflective of the temperature at which the material is used. The solvent is then analyzed for the chemical of interest. FDA (1995) recommends that the solvents used should simulate the food product that will contact the impregnated material. For example, food oils may be appropriate simulants for fatty foods, and 10 percent ethanol may be used as an aqueous food simulant. For migration tests used for non-dietary pesticide exposure assessments, 10 percent ethanol may be an appropriate solvent. Recently, researchers have also been experimenting with artificial saliva and digestive extracts (personal communication between N. Freeman, EOSHI, Rutgers University, and L. Phillips, Versar, Inc., January 7, 1998) that may be appropriate solvents for extracting chemicals from impregnated products that may result in exposure from mouthing behavior. Methods have also been developed for modeling the flux from impregnated materials (U.S. EPA, 1992; U.S. EPA, 1997b). The model uses chemical-specific inputs such as molecular weight, material thickness, migration period, etc. to estimate migration from the material matrix to the surface. For more information on the migration estimation model, see Part D, Chapter 3 - Modeling.

6.2.6 General Considerations for Field Sample Collection

Surface sampling should be conducted in conjunction with air sampling. Enough air samples should be taken in each room to establish a dissipation curve. Duplicate samples at each time period is recommended. Stationary air samplers should be placed as applicable. Control (untreated) samples should be collected from the test site prior to application of the pesticide. Please refer to Part B, Chapter 8 - Inhalation Exposure, for more detailed information such as sampling intervals.

Control or background samples should be collected from the test site prior to application of the test substance. Sufficient control samples should be collected so that fortified controls can be prepared on each sampling day. These fortified controls should be packaged, transported, stored, and analyzed concurrent with the dislodgeable residue samples. (See Part C, Quality Assurance and Quality Control.)

6.3 SAMPLE STORAGE

Indoor surface residue samples and extracts should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis; more detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. The study investigator is responsible for demonstrating the stability of the samples under the storage duration and conditions used.

6.4 SAMPLE ANALYSIS

Dislodgeable pesticide residues should be collected from sampling materials (PUF, denim, etc.) as soon as possible. Validated methods of appropriate or sufficient sensitivity are needed for all sample analyses. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

6.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating dissipation rates, exposure, and risk.

6.6 DATA PRESENTATION

Indoor surface dislodgeable residues should be reported as mg or μg of pesticide active ingredient per m^2 (unit area) of surface area sampled. These data should be reported in tabular form for each sampling day. In addition, the best fit dissipation curve should be plotted (typically log-linear) with indoor surface dislodgeable residues on the Y-axis and time on the X-axis. Distributional data should be presented, to the extent possible.

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PART B - CHAPTER 7
DERMAL EXPOSURE
GUIDELINE 875.2400

7.1 INTRODUCTION

This Guideline provides a description of the techniques commonly used to measure dermal exposure via passive dosimetry. The dermal exposure data generated using this guidance will serve as the basis for regulating chemicals in various settings, including agriculture, industry, and the residential market. This regulation will be based on the exposure and risk assessment process using the data. Additionally, dermal exposure data can be used in conjunction with concurrently gathered ambient chemical dissipation data to establish chemical transfer coefficients. (See Part B, Chapters 3 through 6.) These transfer coefficients can be used in the exposure and risk assessment process to predict exposures for specific activities using ambient residue concentration data in the absence of scenario-specific exposure data (e.g., to develop Restricted Entry Intervals for agricultural harvesters using dissipation data generated in another region).

7.2 SAMPLE COLLECTION

7.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for dermal exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

7.2.2 Timing of Application

Sampling should be conducted during the intended use season or under climatic conditions that are essentially representative of those anticipated during the intended use season. Weather forecasts should be studied, as much as possible, to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. For further information on climatological considerations, see Part B, Chapter 2 - Study Design.

7.2.3 Pesticide Application Rate and Frequency

Generally, the end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate. For example, the typical rate is often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will also provide additional information about the relationship between the application rates, deposition rates, and transfer coefficients. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance should be used.

7.2.4 Sampling Parameters

Sampling parameters should be based on the following criteria:

- A sufficient number of replicates should be generated to address the exposure issues associated with each population of interest. In general, each study should include a minimum of 15 replicates per activity. Where possible, these replicates should be distributed as follows: 5 replicates (i.e., individuals) on each of three monitoring periods (i.e., "n" days after application). Investigators must be flexible concerning the number and distribution (i.e., locations and intervals after application) of the monitoring replicates. Because the aforementioned guideline cannot be expected to apply to all potential scenarios, the Agency requires investigators to submit protocols for review purposes prior to the inception of a study.

- The exposure monitoring period must be of sufficient length to have reasonable detectability of residues on dosimeters, and be representative of a normal activity. The activity must be well defined, and representative of typical practice. Most postapplication activities range from 4 hours (i.e., harvesting roses/chrysanthemums in a greenhouse) to 8 hours (i.e., harvesting strawberries). Thus, a representative monitoring duration based on typical activities is recommended for each replicate. Justifications for determining monitoring durations should be provided in study protocols.

- Changes of clothing, gloves, or samples during the workshift should occur in the case of breakthrough or to coincide with natural breaks in the day. Hand rinse and wash sampling intervals should be instituted when the test subjects routinely clean their hands, at scheduled breaks (e.g., lunchtime) and at the end of the exposure monitoring period. If the representative exposure activity is of a short duration (e.g., 4 hours), one handwash is sufficient.

- Passive dosimetry studies must be carried out concurrently with transferable residue studies. Refer to the appropriate chapters for guidance concerning the types and numbers of transferable residue samples that are appropriate.

- The selected sites and seasonal timing of monitoring must be appropriate to the activity. The need for studies under different geographical/climatological sites should be considered.

- Monitoring should be conducted before residues have dissipated beyond the limit of quantification.

7.2.5 Sampling Techniques

The passive dosimetry techniques for measuring dermal exposure discussed in this Guideline include patches, whole-body dosimeters, hand rinse and wash, gloves, and fluorescent tracer. The selection of the proper technique is dependent upon several factors including activities being monitored, environmental conditions (e.g., heat stress), and physical/chemical properties of the active ingredient.

The Agency recommends whole-body dosimeters instead of patches. However, little to no research has been published to compare and/or validate these two techniques. Both techniques have advantages and disadvantages; the Agency accepts both for outdoor exposure studies. However, whole body dosimeters are essential for proper study of residential indoor exposures. The uncertainties associated with these methods include:

- Protective backing is used in the construction of monitoring patches to prevent the penetration of collected residues. Whole-body dosimeters, however, generally consist of long underwear garments or coveralls worn next to the skin with no protective backing. Due to the lack of an impermeable barrier, the potential for residues to penetrate through whole-body dosimeters exists. This potential could result in whole-body dosimeters underestimating exposure.

- Monitoring patches cover a limited surface area of a body part and are used to extrapolate exposure to the entire body location. Incidental contact or nonuniform deposition of pesticides onto the test subject's monitoring patch can under- or over-estimate exposure (Fenske, 1990). The Agency believes that nonuniformity is less critical in reentry exposure monitoring scenarios because of the physical nature of the contaminant compared to distributional differences noted with pesticide handlers (i.e., because of handling concentrated material).

With respect to monitoring hand exposure by hand rinse/washes, the Agency is concerned about the inadequacy of associated field recovery techniques that start with fortifying the rinsate. Such methodology fails to account for the ability of the dosimeter (in this case, the hands) to trap or retain residues under a variety of environmental and/or physiological conditions. In addition, there is a failure to account for extraction efficiency of the solvent for removing residues from the hand. Fenske and Lu's (1994) findings of handwash removal efficiency indicated that substantial amounts of chlorpyrifos were either absorbed through, or adsorbed to, the skin and that two to five-fold underestimates of exposure may occur. These deficiencies in the monitoring technique may produce an underestimation of actual hand exposure. The use of lightweight cotton glove dosimeters, which may be directly fortified for field recovery determination, minimizes these problems when used for exposure monitoring. Data in the literature indicate that cotton gloves provide a higher residue than the handwashes for the same activity (Fenske et al., 1989, Davis et al. 1983). The Agency recommends that the study investigator address these concerns when selecting and developing a hand exposure monitoring methodology.

Investigators also need to select the location (i.e., inside or outside clothing) of the monitoring devices. If investigators select outside placement of dosimeters, additional uncertainties are built into the risk assessment by the addition of clothing penetration factors. Although the Agency's preferred location of the dosimeters is under typical work clothing, the selected locations should be based on the use scenario. If a typical clothing scenario dictates the need, both internal and external monitors should be used for evaluation of a variety of clothing scenarios.

7.2.5.1 *Patch Dermal Dosimeter*

The patch dermal dosimeter method measures dermal exposure via absorbant patches that are attached to specified areas of a workers body, either inside or outside the clothing. Patches of predetermined size serve as collection media for the pesticide and surrogates for measuring the amount of pesticide contacting the clothing or skin. Subsequent to the performance of postapplication exposure activities, the patches are removed and analyzed for pesticide content. The quantities of pesticide on patches from a specified location on the body are used in conjunction with standard body surface area data for those body parts to estimate potential dermal exposures. Differences between pesticide deposition on inside and outside patches can be used to determine clothing penetration factors. A comprehensive review of the "patch" (i.e., pad) sampling methodology is available in Durham and Wolfe (1962), Wolfe (1976), and Davis (1980).

Patch Composition and Size. The composition and size of the patches used in dermal dosimetry studies are important considerations and should be based on the physical/chemical characteristics of the pesticide and the exposure scenario. For example, patches may be constructed from papermaking pulp (e.g., alpha-cellulose) or a similar material. A high quality alpha-cellulose will absorb a considerable amount of residue without disintegrating. Another material, that is satisfactory and more readily available in small lots, is preparative chromatography paper. Other appropriate materials include surgical gauze, clothing material, and blotter paper. In extremely dusty environments, investigators should consider patch materials that are porous enough to collect dusts or dried residues. Surgical gauze is suggested as an appropriate material for dry formulations. Typically, patch materials should not require preextraction to remove substances that interfere with residue analysis. This should, however, be determined before beginning exposure tests using such patches. Patches should be approximately 1 mm thick and backed with an impermeable material such as aluminum foil, polyethylene, or glassine paper. These materials will reduce the potential for contamination of the patches by materials on the skin or clothing and prevent seepage of collected residues through the patch to the skin or clothing. Multilayered patches are not considered to be suitable for determining penetration. Instead, evaluation of penetration of work clothing should be conducted using inside and outside patches, as described below. Patches should be constructed or used in multiples per sampling location so that the exposed area is approximately 10 cm x 10 cm (100 cm^2). The use of smaller patch areas is generally inappropriate and should be avoided.

Attachment and location of patches. Patches should be attached, according to the exposure situation, to collect residues representative of those impinging on all regions of the body. Normally, a complete set for each exposure period will consist of 10 to 12 patches. Patches should be attached under the test subject's clothing as depicted in Figure B7-1. The patches should be attached directly on the test subject's skin or to the inner clothing. The patches should not be attached to the inside of the outer clothing because these pads would not collect chemicals or residues penetrating through the openings of the clothing. Patches should be attached at the following locations: top of the shoulders, back of the neck just below the lower edge of the collar, the upper chest near the jugular notch, back of the forearms, and front of the thighs and lower legs. Inside patches must be centered under seams as well as under unseamed material, because seams are often the areas of maximum penetration. If the workers are engaged in some activity that is likely to result in extraordinary exposure to regions of the body that are not well represented by the usual patch locations, extra patches must be included to assess such exposure. If the determination of actual penetration of work clothing is desired in the field study, additional patches can be attached to the worker's outer garments. The use of multilayered inside patches is not suitable. Care must be taken to ensure that any patches attached to the outer clothing are near, but not covered by, patches under the clothing. Patches may be attached to the skin using material such as surgical tape which will hold the patches during vigorous activities. Patches may be attached to clothing using safety pins, staples, or tape. Some investigators have utilized specially designed harnesses or lightweight vests fitted with open-fronted pockets to hold the shoulder, chest, and back patches. These

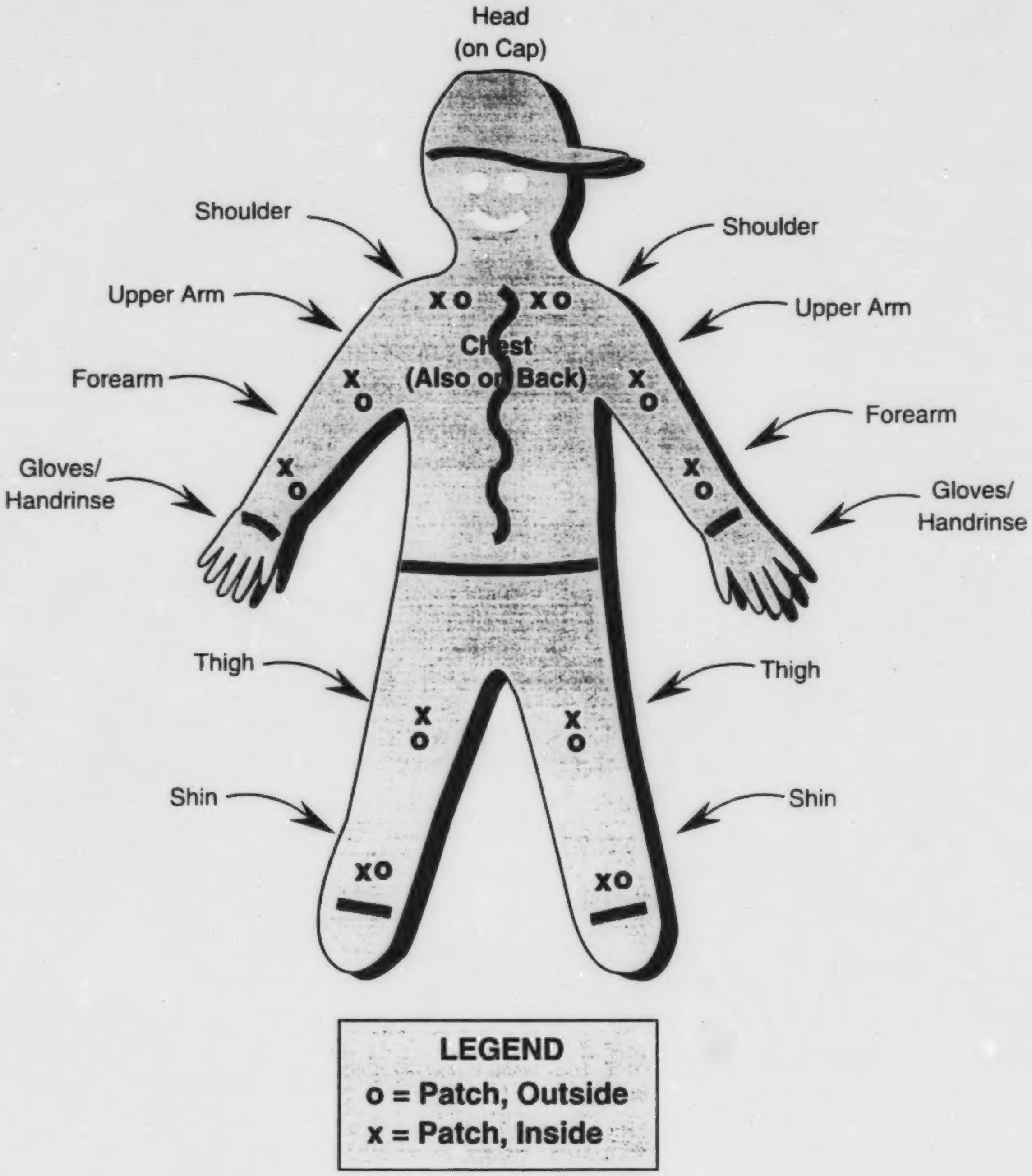
Head
(on Cap)
Shoulder
Shoulder
Upper Arm
Upper Arm
x o
x o
Chest
(Also on Back)
Forearm
Forearm
x o
x o
Gloves/
Handrinse
Gloves/
Handrinse
x o
x o
Thigh
Thigh
x o
x o
Shin
Shin
xo
xo
LEGEND
o = Patch, Outside
x = Patch, Inside

Figure B7-1. Patch Locations

alternative attachment methods have been used successfully and are acceptable. The patches should be evaluated for potential contamination or losses from/to adhesives or holders.

Removal and handling of patches. The procedure for handling exposed patches will depend on the stability of the pesticide(s) being studied. If the prefield study results indicate that the pesticide is stable on moist exposure patches, then the patch should be placed in a prelabeled protective envelope or bag in a manner that avoids both cross-contamination with its holder and residue loss from contact with the envelope. All bags containing exposed patches from one exposure of a single test subject should be grouped together. Care should be taken to not contaminate the patches in handling. If the prefield study results indicate that the pesticide is unstable, the investigator needs to provide a method of handling the patches that is documented prior to the study.

7.2.5.2 *Whole Body Dosimeter*

Another dosimetry method for measuring dermal exposure is the whole body technique. This technique uses a whole body dosimeter to trap pesticides that would otherwise contact the skin. Whole body dosimeters have been used under a variety of circumstances, including for registration purposes. They have also been used as research tools to monitor exposures during specific activities (see discussion of Jazzercise TM, Part B, Chapter 12 - Description of Human Activity).

Composition of the whole body dosimeter. A whole body dosimeter can be defined for the purposes of this document as an article of clothing (including socks) that is useful for monitoring total dermal exposures. It should be constructed of suitable absorbant material such as cotton or cotton/ polyester. Several options are available to investigators (WHO, 1982; Abbott et al., 1987). Standard whole body dosimeters that are generally accepted include commercially available white cotton socks, long-sleeved cotton tee shirts, and thermal underwear bottoms and tops. Whole body "Union" type suits or lightweight coveralls are acceptable to measure exposure as long as the material is of sufficient thickness to avoid penetration that may occur when saturated. Investigators can select the particular articles of clothing from a wide variety of commercially available choices (e.g., sizes, suppliers, fabrics, elastic waist, ankle bands, etc.).

Durability and availability should be considered by investigators as key issues when making selections. The standard dosimeters mentioned above should be capable of withstanding the mechanical forces (e.g., abrasion, snagging, tearing, etc.) exerted during routine activities of the test subjects. Such postapplication agricultural activities may include, but are not limited to, harvesting, maintenance operations, scouting, and planting. Physical durability is critical; if dosimeters are not intact at the end of an exposure monitoring period, they are useless.

Availability of the garments selected as the whole body dosimeters is another critical issue. Investigators must be careful to purchase sufficient quantities of garments to ensure that all dosimeters used in a study for measuring a particular type of exposure are of the same type (e.g., fabric blends) and from the same production lot, if possible. Obtaining dosimeters from the same or similar production lots is critical because it allows direct comparison of exposure results. Also, blanks and fortified samples should be used to evaluate contamination and recovery rates by production lot or batch.

A variation of the whole body dosimeter method uses typical work clothing (i.e., based on the activity and prevailing weather conditions) as the sampling media (Chester, 1993). The advantage of this technique is that exposure may be estimated by dermal dosimetry and biological monitoring simultaneously (Chester, 1993). However, if single layer typical work clothing is used as the dosimeter (i.e., total deposition), a clothing penetration factor will be needed to estimate the amount of residue contacting the skin.

Required facilities. The need for various facilities is self-evident in the discussion of whole body dosimeters. Test subjects must be afforded privacy when donning and removing the garments used as whole body dosimeters. Changing rooms must remain free from contamination with the test substance or other chemical contaminants during preparations for a field trial.

Removal and sectioning of whole body suits. Upon completion of an exposure monitoring period, investigators must be careful to ensure sample integrity. Proper sample collection procedures are critical to minimize loss of test material and prevent contamination of the dosimeters. After exposure, dosimeters should be removed and sectioned for storage, extraction, and analysis. Consideration should be given to turning the dosimeters inside out to minimize loss of test material after removal, based on the type of formulation used. This procedure may be more suitable for liquids than dry formulations since powders may be lost in handling. Investigators must be especially careful to avoid cross contamination of the exposed dosimeters during removal and sectioning. Typically, test subjects will be required to wear total body dosimeters underneath their normal work clothing to simulate the adsorptive/absorptive surfaces of bare skin protected by normal work clothing. Because this is the case, test subjects' normal work clothing will act as a protective "filter" through which the pesticide residues must pass prior to being retained by the dosimeter. As a result, test subjects' clothing must be treated by investigators as being a potential source of cross contamination. Investigators should develop sample collection procedures that minimize cross contamination. For example, to obtain a representative sample, test subjects may be asked to do the following, with assistance of a technician: (1) wear rubber gloves while removing their outer clothing; (2) discard the initial pair of rubber gloves and replace them with a clean pair; then (3) remove and section the total body dosimeter and place it into sample storage containers. At a minimum, whole body dosimeters are typically sectioned by investigators into arms, torso, and legs. Sectioning of dosimeters should also occur in a manner that minimizes cross contamination. Sections should be handled in sequential order of anticipated increasing contamination.

The Agency recognizes that communication between test subjects and investigators is critical. This is never more apparent than when total body dosimeters are collected. Investigators, therefore, are required to be able to communicate clearly with test subjects. Interpreters should be available, if needed. As an example, total body dosimeter samples can easily be invalidated by cross contamination through several mechanisms, including but not limited to, the following examples: (1) test subject places sample on floor or chair in changing room; (2) test subject touches sample wearing rubber gloves used to remove outer clothing; or (3) outside surfaces (i.e., highest anticipated residue levels or nonprotected "skin") of test subject's outer clothing contact surfaces of dosimeter. Post-exposure changing facilities potentially can be highly contaminated with the pesticide(s) being studied because it is normal for test subjects to become dirty during their work activities. Contamination in changing facilities can occur when dirt and dusts retained by the workers' clothing and shoes are shaken off during sample collection procedures.

7.2.5.3 *Hand Rinse and Wash*

Exposure via the hands often accounts for a significant portion of total dermal exposure. Thus, monitoring hand exposures is an important part of a dermal exposure study. Hand rinse sampling has been used for monitoring dermal hand exposure. Prior to conducting a study in which hand rinse techniques are used, participants should be required to wash their hands in an appropriate solvent to remove any background contaminants present.

Materials used. Several types of solutions can be used to collect hand rinse samples. These range from various types of aqueous surfactant solutions to neat isopropanol or ethanol. Investigators are free to select which types of solutions can be used. Investigators, however, must also be careful to consider the physical/chemical properties of the pesticide(s) being studied. For example, if a pesticide is water soluble, then an aqueous surfactant solution should be used instead of a neat alcohol (i.e., octanol water partition coefficient (K_{ow}) may be used as an indicator of a chemical's water solubility). Sufficient quantities of hand rinse solutions should be prepared prior to field trials to avoid the chance of cross contamination during solution preparation in the field.

Water used for preparing aqueous solutions should be distilled and deionized; however, either deionized or distilled water is sufficient if no alternatives exist. Water, used in the preparation of the aqueous surfactant solutions, may be purchased from commercial vendors. If commercial water is used, investigators should try to obtain sufficient quantities from the same lot and supplier. If the water used in a study is tapwater purified by the performing laboratory (i.e., distilled and/or deionized), the equipment used to prepare the water must be described in the report. Investigators must be careful to use the same water source throughout all phases of a study. Several commercially available surfactants can be used to prepare hand rinse solutions (e.g., Sur-Ten, Aerosol OT-75, and Nekal WT-27). In general, hand rinse solutions should be diluted and otherwise prepared in a manner congruent with that described for the dislodgeable foliar residue solutions. (See Part B, Chapter 3.)

Neat alcohols (e.g., isopropanol or ethanol) may also be used as hand rinse solutions. The same factors described above regarding the purchase/preparation of water for use in the aqueous hand rinse solutions also apply to alcohols. Investigators must use pesticide grade solvents if neat alcohols are to be used as hand rinse solutions.

Sampling procedure. Investigators use a wide array of techniques to obtain hand rinse samples. Some investigators opt for minimal mechanical agitation, while others routinely employ it in their sampling methods. The Agency, however, recommends that mechanical agitation be used. Various procedures can be used to introduce agitation and, therefore, theoretically, mechanical removal of residues from the skin's surfaces (Durham and Wolfe, 1962). These procedures can include, but are not limited to: (1) a hand rinse procedure in which test subjects wash their hands in a routine fashion, or (2) a procedure in which hands are placed in individual polyethylene bags containing a hand rinse solution and are then shaken vigorously for at least 2 minutes. All field procedures must be carefully documented in any submission to the Agency.

7.2.5.4 *Sampling Gloves*

Gloves provide investigators with an alternative technique for monitoring dermal hand exposure. As with the hand rinse technique described above, participants should be required to wash their hands in an appropriate solvent to remove background contaminants before putting on the dosimeter gloves. If protective gloves are worn by the study participants, dosimeter gloves should be worn underneath.

Materials. A wide variety of lightweight absorbant cloth gloves are commercially available. Durability and availability should be considered by investigators as key issues when selecting a glove for use as a field dosimeter. Physical durability is critical; if the gloves are not intact at the end of an exposure monitoring period, they are useless. The standard dosimeters should be capable of withstanding the mechanical forces (e.g., abrasion, snagging, tearing, etc.) exerted upon them as a result of the routine activities of the test subjects. Such postapplication activities may include harvesting, maintenance operations, scouting, and planting. While white "pall bearers" gloves have a number of advantages as hand dosimeters, they lack the physical strength for some activities. Various knit gloves (sometimes labeled "pickers gloves") are a more rugged alternative. As with all dosimeters, gloves should be pre-tested to ensure that they do not contain materials that might interfere with the pesticide residue analysis.

Availability of the selected gloves is another critical issue. Investigators must be careful to purchase sufficient quantities of gloves to ensure that all dosimeters used in a study for measuring a particular type of exposure are of the same type (e.g., fabric blends) and from the same production lot, if possible. Obtaining gloves from the same or similar production lots is essential because it allows direct comparison of exposure results.

Removal of sampling gloves. Upon completion of an exposure interval, investigators must be careful to ensure the integrity of the samples. Proper sample collection procedures are critical. Investigators must develop sample collection procedures that prevent cross contamination. For example, to obtain a representative sample, test subjects should peel the gloves away (i.e., turn inside out) from both hands, then place the gloves into a sample storage container(s).

7.2.5.5 *Fluorescent Tracer*

Dermal exposure can be quantified indirectly and non-invasively by measuring deposition of fluorescent materials. The use of fluorescent compounds can be coupled with video imaging measurements to produce exposure estimates over virtually the entire body (Fenske et al., 1986a, 1986b 1993). This requires pre- and post-exposure images of skin surfaces under longwave ultraviolet illumination, development of a standard curve relating dermal fluorescence to skin-deposited tracer, and chemical residue sampling to quantify the relationship between the tracer and the chemical substance of interest as they are deposited on skin. Imaging analysis has been applied primarily to pesticide mixers and applicators (Fenske, 1988; Methner and Fenske, 1994a, 1994b), but has also been applied to workers handling treated lumber (Fenske et al., 1987), to children contacting turf following tracer applications (Black, 1993), and to greenhouse applicators (Archibald, 1995).

Ideally, this method could provide improved accuracy in dermal exposure assessment because it measures actual skin loading levels (i.e., the skin serves as the collection medium) and it is extremely sensitive in a qualitative fashion. In practice, however, it has several important limitations: (1) use of a tracer requires the introduction of a foreign substance into the production system; (2) the relative transfer of the tracer and chemical substance of interest must be demonstrated during field investigations, (3) additional quality assurance steps may be required during field studies, including range-finding and the evaluation of potential tracer degradation due to sunlight; and (4) when protective clothing is worn, separate studies may be required to determine the relative fabric penetration of the tracer and the chemical substance of interest. Important considerations in the use of fluorescent tracer technique include the following: (1) performance of the tracer/dye as a suitable surrogate should be tested prior to use in the field study, (2) the tracer/dye should not alter the physical properties of the pesticide formulation, and (3) the clothing penetration features of the tracer/dye should be the same as those of the pesticide.

7.2.6 General Considerations for Field Sample Collection

Sufficient control samples should be collected so that fortified controls can be prepared on each sampling day. These fortified controls should be packaged, transported, stored, and analyzed concurrent with the dermal exposure samples. (See Part C, Quality Assurance and Quality Control).

7.3 SAMPLE STORAGE

Samples should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis; more detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. The study investigator is responsible for demonstrating the stability of the samples under the storage duration and conditions used.

7.4 SAMPLE ANALYSIS

Validated methods of appropriate or sufficient sensitivity are needed for all sample analyses. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

7.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating exposure and risk.

7.6 DATA PRESENTATION

Individual body locations and total residue data should be reported in tabular form. The residues should be reported as μg or mg of pesticide active ingredient per body part sampled if generated using the whole-body dosimetry technique and on a surface area basis if the data were generated using the patch technique (i.e., normalized on patch sample surface area; ug/cm^2 or mg/cm^2). Distributional data should be provided, to the extent possible.

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PART B - CHAPTER 8

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PART B - CHAPTER 8
INHALATION EXPOSURE
GUIDELINE 875.2500

8.1 INTRODUCTION

This Guideline provides a description of the techniques that can be used to measure inhalation exposure and ambient air concentrations of pesticides. The data obtained are needed to assess risks associated with the inhalation of airborne particulates containing pesticide residues and gases/vapors resulting from the previous application of a pesticide product (i.e., to assess postapplication inhalation exposures).

8.2 SAMPLE COLLECTION

This section describes the sample collection procedures required for developing inhalation exposure data. See Part B, Chapter 2 - Study Design, for more details pertaining to protocol development and study conduct.

8.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

8.2.2 Timing of Application

Sample collection should be conducted during the intended use season or under climatic conditions that are essentially identical to those encountered during the intended use season. Weather forecasts should be studied to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. For further information on climatological consideration, see Part B, Chapter 2 - Study Design.

8.2.3 Pesticide Application Rate and Frequency

Generally, the end-use product chosen for the study should be applied at the maximum rate specified on the label. Monitoring at more than one rate will provide additional information about the relationship between the application rates and exposure concentrations. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance should be used.

8.2.4 Sampling Parameters

Sampling parameters should be based on the following criteria:

- A sufficient number of replicates should be generated to address the exposure issues associated with each population of interest. In general, each study should include a minimum of 15 replicates per activity. Where possible, these replicates should be distributed as follows: 5 replicates (e.g., individuals) on each of three monitoring periods (e.g., "n" days after application). Investigators must be flexible concerning the number and distribution (e.g., locations and intervals after application) of the monitoring replicates. Because the aforementioned guideline cannot be expected to apply to all potential scenarios, the Agency requires investigators to submit protocols for review purposes prior to the inception of a study.

- The exposure monitoring period must be of sufficient duration, and the analytical method must have adequate sensitivity to ensure that each monitored activity has been sufficiently evaluated . Minimum sample volume and analytical quantification limits should be reflective of appropriate toxicology endpoints. (See Part C - QA/QC for a discussion of determining appropriate limits of quantification). The activity must be well defined and be representative of typical practice. Most postapplication activities range from 4 hours (e.g., homeowner lawn and garden maintenance) to 8 hours (e.g., harvesting strawberries). Thus, a representative monitoring duration based on typical activities is recommended for each replicate. Justifications for determining monitoring durations should be provided in the study protocol.

- Inhalation exposure studies must be carried out concurrently with dermal exposure and transferable residue studies. Refer to the appropriate chapters for guidance concerning the types and numbers of transferable residue and dermal samples that are appropriate.

- The selected sites and seasonal timing of monitoring must be appropriate to the activity.

- When appropriate to conduct ambient (i.e., area or stationary) monitoring in conjunction with, or in lieu of, personal monitoring, each study should contain sufficient samples to characterize the likely range of possible exposure concentrations resulting from the use of the chemical of interest. Guidance on sampler location is included in this chapter. Additionally, samples should be collected to ensure that the reentry exposure scenario can be addressed with the resulting data (e.g., sampling should be completed concurrently with harvesting activity).

- Along with gas and vapor phase monitoring, total (i.e., rather than respirable) airborne particulate levels should be monitored in all scenarios unless there is justification for doing otherwise. Typically, the Agency is concerned with quantifying total airborne concentrations of materials as opposed to quantifying only inspirable or respirable fractions of airborne contaminants because of the potential for the absorption of chemical residues via the upper respiratory tract and/or through the gastrointestinal tract. The relationship between particle sizes and inhalation exposure is illustrated in Figure B8-1.

8.2.5 Monitoring Selection Criteria

8.2.5.1 *General Considerations*

Selecting the proper method for monitoring inhalation exposure depends on several factors including, but not limited to, the following: (1) typical pesticide usage practices; (2) the range of air concentration anticipated; (3) minimum quantification limit required; (4) the anticipated durability of the devices/dosimeters under consideration; (5) the physical and chemical properties of the pesticide (e.g., stability and vapor pressure); (6) the anticipated physical state (e.g., gas, aerosol, particulate) of the airborne contaminant; and (7) sampling device flow rate (as applicable).

The Agency recognizes that there are shortcomings inherent with the use of almost any monitoring technology. Understanding the conditions under which the pesticide is used and the practices associated with its use will contribute greatly to the investigator choosing the appropriate monitoring method. A principal concern related to the monitoring of airborne pesticide residues is the anticipated physical nature in the ambient environment after the application of a pesticide product.

Investigators must select the equipment and sample matrices that are to be used in any study by careful consideration of the general criteria described above and considering both the positive and negative attributes of each type of sampling equipment/matrix.

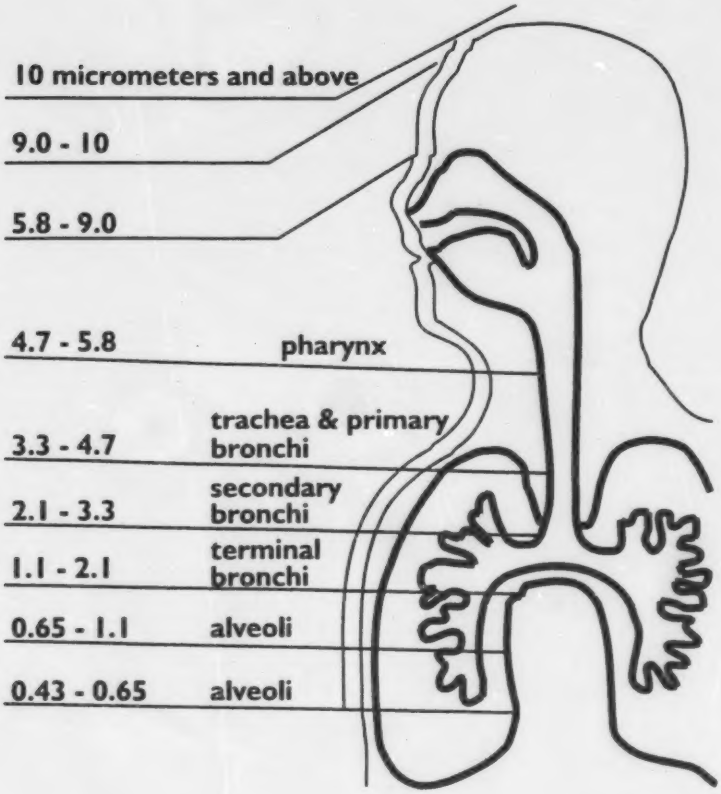
10 micrometers and above
9.0 - 10
5.8 - 9.0
4.7 - 5.8
pharynx
3.3 - 4.7
trachea & primary bronchi
2.1 - 3.3
secondary bronchi
1.1 - 2.1
terminal bronchi
0.65 - 1.1
alveoli
0.43 - 0.65
alveoli

Figure B8-1. Relationship Between Particle Size and Deposition in the Respiratory Tract

Source: Graseby Anderson, 1985.

8.2.5.2 *Method Sensitivity*

The investigator will need to anticipate what the maximum and minimum expected concentrations may be in the field over the time period of interest, whether levels are likely to vary significantly during the sampling period, and whether the chosen methodology can be expected to be adequate to deliver the required information under actual field conditions, given the nature of the contaminants being monitored. For more information on the selection of maximum detection limits, see Part C - QA/QC.

Additional guidance is available from several sources on the health-based limits associated with various chemicals. These values may be useful in determining the range in which detection/ quantification limits need to be set. For an occupational exposure study, it is appropriate to consult: (1) The Occupational Safety and Health Administration's (OSHA's) Permissible Exposure Limits (see 29 CFR 1910.1000) for legal limits; (2) American Conference for Government Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) (ACGIH, 1996); and (3) the National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards (NIOSH, 1994b). The NIOSH Recommended Exposure Limits are guidelines only and are not legally enforceable. Although ACGIH TLVs do not have the force of law either, they are peer-reviewed, well-accepted, and widely used guidelines. OSHA's ongoing 1970 PELs were in fact adopted from the ACGIH TLVs of that day. A complete discussion of the derivation of the TLVs is available in ACGIH (1991).

8.2.5.3 *Sampling Pump Flow Rates*

Establishing the proper flow rate is critical to the design of any inhalation exposure study. Minimum flow rates can be calculated in advance based on anticipated exposure monitoring periods, anticipated collection efficiency (if available), and the quantification limit of the analytical method. If the flow rate is too low, an insufficient sample volume will be collected over the specified exposure monitoring period; or the chemical residue may not be collected on the sorption media. If the flow rate is too high, the pump battery charge may be inadequate to last an entire exposure monitoring period, and excessively high flow rates may result in sample losses or artifact formation. Furthermore, when sampling particulates, it is important to consider capture velocities. Flow rates or sampling times may need to be adjusted when monitoring in an area containing extremely high contaminant concentrations (e.g., due to filter overloading). Additionally, recommendations from sampling media manufacturers should be heeded when defining flow rates (e.g., several sorbent tube manufacturers limit flow rates - generally 1 Lpm or less).

8.2.5.4 *Method Validation Considerations*

The investigator bears the primary responsibility for the choice and proper application of an appropriate sampling and analytical methodology. When designing a study, it is recommended that investigators review available methods contained in several sources of validated sampling and analytical methods (NIOSH, 1994a; OSHA, 1990; OSHA, 1993; ASTM, 1996; ASTM, 1997a; ASTM, 1997b). However, it must be stressed that available methods were likely developed for application in an occupational setting. Therefore, they may not be sensitive enough for residential exposure scenarios.

If the investigator finds that a pre-validated methodology from a recognized, peer-reviewed, source is not available for the pesticide analyte of interest, or if an available pre-validated methodology is not sensitive enough, then the study design will need to include data which demonstrate the validity of the chosen method under the conditions of the study. This is particularly likely to be necessary if the method chosen is a proprietary, unpublished method, or a method available in the general published literature. For information on standards used by NIOSH, OSHA, and ASTM for data validation, the reader should consult published methods found in NIOSH (1994a), OSHA (1990), and ASTM (1997).

Development of an inhalation exposure monitoring method should include three phases: (1) selection of several sample collection protocols to be considered for validation, based on the physical nature of the contaminant (e.g., particulate or vapor), a literature review, Agency recommendations, experience, etc.; (2) performance of a rangefinder retention/breakthrough (e.g., volatilization) study to narrow the selection process; and (3) final method validation based on a definitive pre-field phase breakthrough/retention study and an in-field recovery study. (See Part C - QA/QC.)

8.2.5.5 *Study Validation Requirements*

At least two critical validation requirements must be completed for every study. These are: (1) pre-field phase retention and breakthrough/volatilization trials and (2) field recovery studies.

Retention. Retention efficiency studies are required to validate the performance of sample collection media prior to field trials. Retention samples are inhalation sampling media that have been fortified with several concentrations of the analyte of interest, allowed to dry for a sufficient time (e.g., to permit solvent evaporation from fortifying solution to prevent volatilization due to coevaporation of analyte with solvent), and that have had air drawn through them for a period of time, at a flow rate similar to that anticipated in the field study under similar conditions. Tests must be performed at high residue levels (e.g., 10x and 100x to 1,000x LOQ) to accurately determine the percentage of retention that will occur. These samples, coupled with breakthrough samples described below are intended to assess the utility and performance of the methodology.

Breakthrough. Breakthrough samples are blank (e.g., not fortified) sample collection media that have been placed in-line between the fortified retention sampling media and the pump (e.g., personal sampling pump) to entrap residues which may volatilize from the fortified media. (Melcher et al., 1978) Tests must be performed at high residue levels (e.g., 10X and 100X to 1,000X LOQ) to accurately determine the percentage of breakthrough that will occur. Low concentrations make it more difficult to accurately quantitate breakthrough levels because anticipated levels may approach the LOQ or LOD and make quantification of available residues difficult. Note that the same technique should be routinely employed during field sampling, as a quality control measure to ensure that collected chemical residues are not lost from the media during sampling. According to standard industrial hygiene practice, if the back-up section contains more than 20 percent of the concentration in the front part of the tube, the sample should be considered suspect (NIOSH, 1980; ACGIH, 1995; OSHA, 1995).

Retention and breakthrough studies should be performed under conditions similar to those anticipated in the field phase of the study. Laboratory incubators can be used to simulate field temperature and humidity conditions. If environmental conditions are anticipated to change during exposure monitoring periods, then a worst-case scenario (e.g., most chances for volatilization and degradation) should be simulated (e.g., relative humidity typically drops drastically in the San Joaquin Valley of California as the sun rises). Worst-case scenarios should be supported by investigators based on the physical/chemical characteristics of the pesticide(s) being studied.

Field Recovery. Inhalation monitoring media are fortified and allowed to dry as above, then exposed to identical environmental conditions as the actual field samples (e.g., all tests done concurrently). Air is drawn through them at flow rates and volumes similar to actual field samples. Field recovery samples are required in conjunction with any retention/breakthrough study to determine the effect of ambient environmental conditions (e.g., volatilization and other dissipation or degradation effects) on the field recovery of residues collected on the inhalation monitoring media. (See Part C - QA/QC for further details.)

Trapping Efficiency. While it would be desirable to know the trapping efficiency of media using actual airborne particulates containing the chemical analytes of interest, no completely satisfactory procedure is currently available for this type of testing. Investigators are strongly urged to develop and enhance procedures for determining trapping efficiency. Unless the chemical of interest can be introduced directly to test the sample media, investigators will have to determine the retention efficiency of fortified media rather than the trapping efficiency as described for the retention/breakthrough samples above.

8.2.5.6 *Novel Sampling and Analysis Methodologies*

Although the Agency encourages investigators to develop and use novel approaches for monitoring inhalation exposure levels, the Agency would like the opportunity to review and approve such technologies prior to the initiation of any field experiments. Historically, investigators have developed protocols based on the types of monitoring techniques that they have used most often (e.g., personal sampling pump in conjunction with a filter cassette and resin tube). Investigators must determine and justify their selections of specific sampling methods, the appropriate sampling medium, conditions for storage of samples, and analytical procedure (NIOSH, 1995). Investigators should make selections based largely on the pesticide(s) and use patterns being studied. Additionally, as indicated above, investigators may need to develop sampling regimens that are capable of monitoring both gas phase and particulate airborne contaminants (NIOSH, 1984).

8.2.6 Sampling Techniques

This section describes the available sample collection techniques, monitoring equipment, and sampling media that can be used in obtaining inhalation exposure data. Where possible, recommendations are also made with regard to the selection of specific techniques that could be used to evalulate specific exposure scenarios. See Part B, Chapter 2 - Study Design for further information pertaining to protocol development and study conduct. The Agency prefers that personal sampling be conducted using personal sampling pumps, and sampling trains consisting of filter cassettes and resin tubes or polyurethane foam filters. The Agency considers personal sampling to be appropriate for most occupational exposure scenarios and for some residential scenarios. In cases where personal sampling is not appropriate, the Agency requires that stationary sampling be conducted using equipment/matrix combinations that maximize the potential sample volume collected for that scenario. Passive monitors may be used under certain circumstances, as appropriate (e.g., volatile compounds). Use of grab sampling or direct technologies may also be useful in specialized situations. Further information is available in ACGIH, 1995; National Safety Council, 1996; NIOSH, 1995; OSHA, 1995; Lodge, 1989).

8.2.6.1 *Personal vs. Area Monitoring Techniques*

Both personal and area monitoring can provide airborne concentration data that may be useful in the risk assessment process. Personal monitoring is generally performed using battery-powered pumps/devices, which generally operate within a range of flow rates. Area monitoring (also known as stationary monitoring) can be performed using personal sampling pumps; mid- and high-flow rate stationary air samplers; grab sampling devices; passive monitors; or direct-reading instruments. Specific requirements of each approach and the corresponding inadequacies are addressed below. Additionally, general requirements that are pertinent to either approach are also presented.

Personal Monitoring. The Agency considers the use of battery powered, personal sampling pumps to be the most effective method for quantifying inhalation exposure levels. Investigators should use personal air sampling pump methods unless it has been determined that this approach would not be effective or there is a more effective approach available. Personal sampling pumps should be attached to test subjects in the least obtrusive, most comfortable manner possible. For the test subject's comfort and safety, it is necessary to ensure that the pumps, hoses, and sample media are secured to minimize movement/shifting and the potential for snagging. For the vast majority of exposure scenarios, the use of personal sampling pumps will be the most appropriate. In certain specialized situations, other devices such as passive monitors, may be appropriate. Manufacturers of passive monitors generally provide very explicit direction concerning the scenarios that are appropriate for their use.

Devices which contain the sampling media attached to personal sampling pumps (e.g., 37-mm cassettes containing filters in conjunction with the appropriate resin tube or cylindrical holders containing PUF plugs) should be clipped to the collar in the breathing zone of test subjects so that the sample air inlet is facing slightly downward whenever possible (ACGIH, 1995; OSHA, 1995).

Area Monitoring. Area monitoring provides another potentially useful approach for quantifying ambient air levels that may be useful in the risk assessment process. Several types of equipment and sample media combinations can be used during area monitoring studies (e.g., high-volume air samplers, personal sampling pumps, passive monitors, grab sampling, and alternative technologies such as real-time gas chromatography). If area monitoring is performed, samples should generally be collected within the treatment area. [There are notable exceptions such as after public health applications of mosquito control agents.] Additionally, samples should be collected in zones of the treatment area that are typical of the exposure scenario being monitored. For example, samples should be collected from the center of a chemically treated field and from at least four other locations, preferably at the cardinal compass points from the center location (e.g., recreational turf application on parkland). (See Figure B8-2.) Note that appropriate climatological data must also be collected concurrently with any stationary air sampling as described in Part C.

Indoor sampling strategies should be designed based on the nature of the exposure scenario and the building construction type (e.g., for residences: plenum, slab, crawl space, or basement). Investigators must be careful not to design a study in which sampled indoor air will be altered by

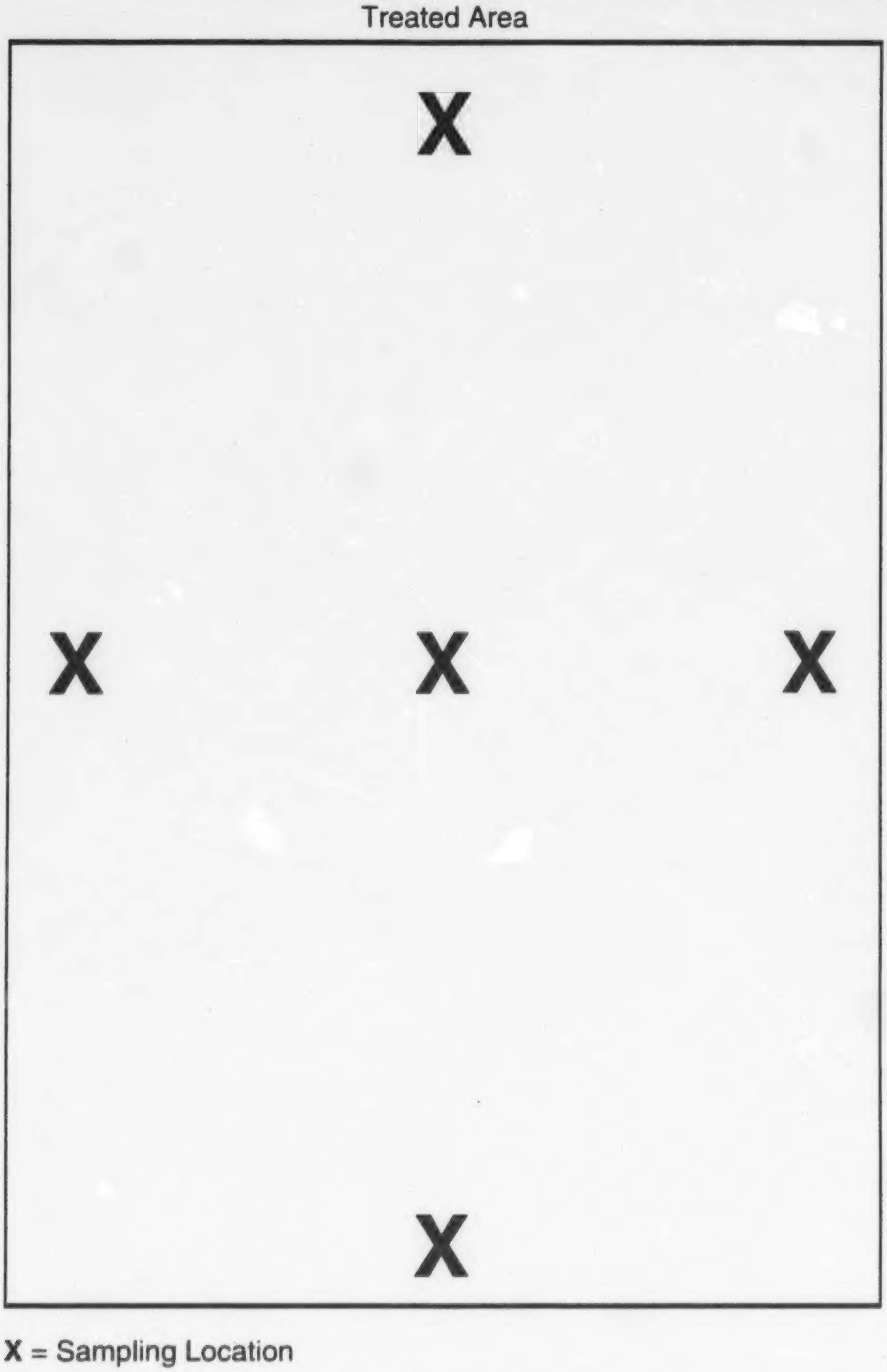
Treated Area
X
X
X
X
X
X = Sampling Location

Figure B8-2. Suggested Outdoor Stationary Sampling Regimen

scavenging or cleaning the ambient air near the sampler or by altering any airflows or mixing conditions within the residence. Additionally, for indoor scenarios, samples should be collected at heights that represent the breathing zones of infants/children and adults (e.g., 18 and 48 inches). Generally, it is recommended that indoor air monitoring protocols be developed after consultation with the Agency.

8.2.6.2 *General Considerations*

Various issues must be addressed in the design of an inhalation exposure monitoring study regardless of whether the study is performed using a personal or stationary monitoring approach.

Equipment Maintenance. Air samplers are mechanical devices. As a result, they can be expected to break down during use or otherwise malfunction (e.g., overheating, calibration adjustments, power supply failures, etc.). Investigators should anticipate these occurrences and take the appropriate precautions. Mechanical air samplers should be maintained according to manufacturer specifications.

Sample Integrity. Sampling media must remain intact throughout the duration of an exposure monitoring period to ensure the integrity of the sample. Therefore, sampling media must be designed and used in a manner that is consistent with: (1) the sampler's surviving the exposure monitoring period intact; (2) obtaining a valid, representative sample; and (3) not interfering with the normal work functions of the test subjects. If a sample should leak, spill, tear, or otherwise disintegrate during the exposure monitoring period, the investigator should assume that the integrity of the sample is compromised. If the sample is compromised, it must be identified as such and, in most cases, should be voided. For example, monitors can be reattached to clothing or replaced with a fresh, unexposed monitor as long as it is accompanied by appropriate documentation.

If samplers break or otherwise obviously malfunction during operation, the devices should be replaced and the sampling should continue, if the integrity of the sample can be assured. The investigator should use any means available to obtain field samples when malfunctioning equipment is involved unless the integrity of the sample is unquestionably compromised (e.g., discretion is called for on the part of the investigator). If questions regarding the integrity of the sample cannot be answered, the sample should be discarded or any results based on that sample must be explained with the appropriate caveats.

Sample Volume. Studies should be designed to maximize the duration of the sampling interval and air flow rates within the appropriate flow rate range in order to increase the potential for capturing enough of the chemical of concern in a sampling event to be quantifiable (e.g., the total sample volume should be maximized as appropriate).

Sampling Pump Calibration. It is necessary to check flow rates at the beginning and end of each exposure monitoring period. Several types of equipment are available for calibrating inhalation exposure monitoring equipment. All equipment used to calibrate personal sampling pumps must be a primary standard or be traceable to a primary standard (e.g., electronic soap film meters or dry gas meters). A rotameter may be used as a secondary method in the field provided it is traceable to a primary standard. If flows change during the exposure monitoring period, the mean flow rate should be used for all calculations unless otherwise justified by the investigator. The flow rate must always remain within the acceptable flow rate range determined for that sampling method (e.g., changes in air flow over the monitoring period must be minimized or a sample is considered invalid; acceptable variations in air flow rate is generally limited to ±10 percent).

Airflow rates should be recorded at the initiation and termination of the monitoring period, with the average being used in all calculations unless otherwise justified by the investigator. Intervals where the sampling process has been interrupted should be described in submissions to the Agency (e.g., fueling portable gasoline powered generators to operate air samplers, changing filters, checking flows, etc.).

8.2.6.3 *Monitoring Equipment*

Several types of equipment are available to monitor inhalation exposure levels. The most commonly available types are described below and in ACGIH (1995) and National Safety Council (1996) . Each type of equipment, when used in conjunction with the proper sample collection media, can be used to monitor inhalation exposure levels to airborne chemical residues. Each type of equipment has particular applications and limitations associated with its use.

Personal Sampling Pumps. Several brands of commercially produced, battery-powered, personal sampling pumps are available for use in monitoring inhalation exposure. These pumps typically consist of a battery-powered motor that operates a diaphragm pump capable of performing for up to 8 hours at air flow rates in the 1.0 to 4.0 L/minute range. Modern personal sampling pumps often have the capability to maintain a flow rate set point, within a specified tolerance (e.g., ±10 percent) that adjusts to the actual pressure drop across the sampling media even as head pressure fluctuates due to loading on the sampling media. Additionally, these modern devices electronically record flow rates and sample times for exposure intervals. Most sample collection methods are based on flow rates that range from 0.5 to 2.0 L/minute.

High Volume Monitoring Pumps. Several brands of commercially produced sampling pumps are available for use in monitoring ambient airborne chemical residues. These air samplers are usually based on one of two common designs. The first design is a high volume, centrifugal, electric-powered fan that draws air through a filter directly attached to the device at flow rates ranging from 20-50 ft^3/minute (CFM) or >250 LPM (e.g., as described in ASTM, 1996 or 40 CFR 50). The second common type of stationary monitor is the rotary-vane vacuum pump that can typically operate at lower average flow rates (e.g., "Anderson" 1 CFM sampler). Higher flow rate stationary air samplers should be selected and used with caution so not to modify the sampled environment by scavenging/cleaning the air within that environment (e.g., inside residences).

Passive/Diffusion Monitors. Passive monitors are commonly used by industrial hygienists and other health and safety personnel to monitor ambient levels of certain highly volatile workplace gases and vapors, generally indoors (e.g., 3M-type and polyacrylate film fiber by Supelco). (See Figure B8-3.) These devices should be used with caution in pesticide exposure studies for two reasons: (1) most pesticides are insufficiently volatile and/or have diffusion coefficients which are too low for efficient collection, and (2) passive dosimeters measure only gas and/or vapor phase contaminants (i.e., particulate or particulate-bound residues are not quantified). It is recommended that the manufacturers of these devices be consulted for technical assistance when considering the use of these devices for pesticides because of the limitations associated with their use. Generally, the primary concern over the use of passive monitors is the lack of appropriate validation data for the chemical of concern, including the accuracy and precision of the dosimeters.

Direct-reading Technologies. Investigators are encouraged to also consider using other approaches for monitoring inhalation exposure levels and/or ambient air concentrations, when appropriate. Direct-reading technologies may include direct-reading instruments (e.g., portable gas chromatography; real time aerosol monitoring; colorimetric tubes commonly used in industrial hygiene; or immunoassay techniques). Thorough documentation must be provided to justify the use of direct-reading technology.

Grab Sampling. Grab sampling should only be used in environments where other technologies are not functional or the use of this approach can be otherwise justified. This technique, which is only applicable to collection of samples containing volatile compounds in the gas phase (e.g., sulfuryl fluoride, methyl bromide), involves drawing a bulk volume of air into a sample collection container (e.g., bag or metal canister) either passively or actively (e.g., using a pump), followed by laboratory analysis and quantification of the analyte in the laboratory. Grab sampling is not intended for environments where airborne particulate contaminants are of concern. Samples can be retained and analyzed by a direct method or the captured residues can be trapped on a sorbent and then analyzed.

Several sample collection containers are commercially available that are appropriate for bulk sampling purposes. These containers are of known volume and are typically made from a well characterized

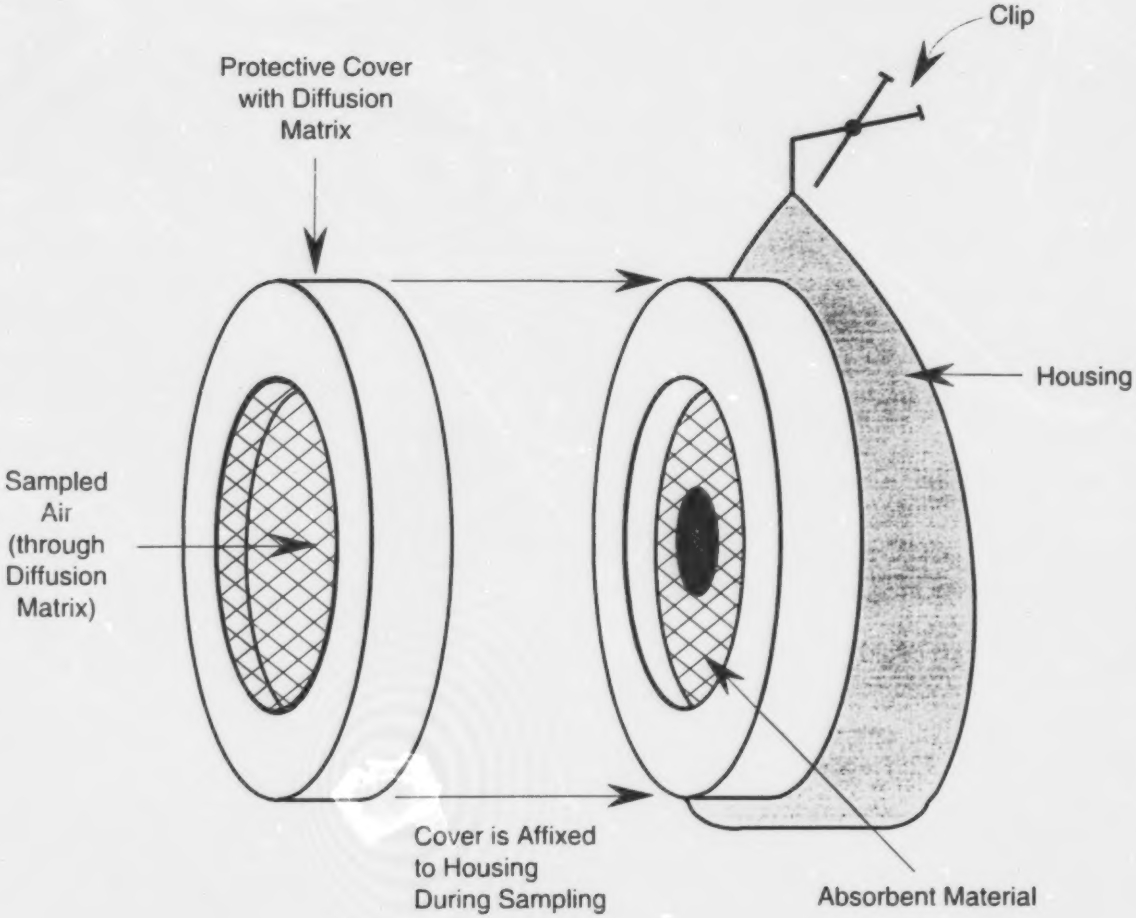
Clip
Protective Cover
with Diffusion
Matrix
Housing
Sampled
Air
(through
Diffusion
Matrix)
Cover is Affixed
to Housing
During Sampling
Absorbent Material

Figure B8-3. Schematic of Typical Passive Monitor/Badge

material (e.g., mylar, polyethylene bags, or evacuated stainless steel canisters). Flow rates are not as important in this technique, since the purpose is to collect a bulk sample and not to characterize inhalation exposure levels over the duration of the exposure monitoring period.

8.2.6.4 *Sampling Media*

A large variety of sampling media are available to monitor inhalation exposure and ambient air concentrations. Various types of media and sample holders are described below. In general, (1) filters or membrane filters (e.g., mixed cellulose ester, glass fiber, PVC, etc.) are used to trap particulates; (2) sorbent resins (e.g., silica gel, activated charcoal, Chromosorb, etc.) are used to trap gases and vapors; (3) PUF (e.g., polyurethane plugs) is useful to trap particulates as well as gases and vapors (combinations of filters and sorbent resins in series are an acceptable alternative); (4) particle sizing devices may be employed to differentiate total particles from respirable particles; (5) evacuated sample collection vessels (e.g., Tedlar bags or metal canisters) may be useful to monitor gaseous fumigants (e.g., methyl bromide or sulfuryl fluoride). One other sampling medium is briefly discussed reflecting its limited applicability. Glass impingers containing trapping solutions are occasionally, but rarely, employed in pesticide monitoring studies. For summarized information on recommended techniques and equipment to use to analyze specific analytes, investigators may consult OSHA (1991).

Identifying the most suitable medium for a particular investigation will depend on the physical/chemical properties of the analyte. Investigators must rationalize the selection and use of a method that is not designed to simultaneously collect both gas/vapor and particulate phase contaminants in any study. For most exposure scenarios, the Agency believes there may be a potential hazard/risk from both gaseous phase or particulate airborne contaminants (NIOSH, 1984).

Many sample holder devices are available for the different types of media used for entrapping airborne chemical residues while monitoring inhalation exposure levels including, but not limited to, the following: spill-proof microimpingers; 37-mm cassettes containing a filter; glass tubes that contain various sorbent resins; and plastic/glass tubes to contain polyurethane foam plugs. Most sample holders are of the same general design: a fitting for attachment of flexible tubing at each end of the holder (e.g., to attach personal sampling pump and resin tube used in series); rubber grommets to hold the resin tube in place at both ends of a metal holder that allow air to flow across the resin bed and that hold the tube in place; and an alligator-type clip to affix the device to the test subject during sampling. (See Figure B8-4.)

Sorbents. A wide variety of sorbents are available for use as inhalation monitoring media. These sorbents are typically contained in small diameter glass tubes, approximately 10 cm in length, that are open at both ends to allow air flow through the sorbent bed. (See Figure B8-4.) Sorbent tubes are usually designed only for the measurement of airborne chemical residues present as a gas or vapor. Additionally, these devices are typically designed exclusively for use in conjunction with a personal sampling pump. A large variety of sorbents are available in commercially produced tubesincluding, but are not limited to, the following: XAD, chromosorb, tenax, silica, alumina, activated charcoal, and florisil. Flow rates for personal sampling pumps typically average 0.8 to 1.0 L/minute when sampling with these devices.

Filters and Membrane-filters. Filters, for the purposes of this guideline, are porous structures with definable external dimensions such as thickness and cross section normal to laminar air flow. Filters remove particles from a gas stream by various mechanisms depending on flow rate, structure of the filter, and the nature of the contaminant. One of the oldest and most common filter types is the fibrous filter, which is comprised of mats of cellulose, glass, quartz, asbestos, or plastic fibers in random orientation within the plane of the filter sheet. A wide variety of commercially produced filters are available. Common filter types include, but are not limited to, the following: mixed alpha-cellulose ester, glass fiber, and coated filters (e.g., charcoal impregnated).

According to ACGIH (1995), "the term "membrane filter" was originally applied to discs of a cellulose ester gel having interconnected pores of uniform size. Gel type membrane filters are now also available in polyvinyl chloride (PVC), nylon, and other plastics. The Nucleopore® filter, a polycarbonate pore filter, is generally considered to be a membrane filter, but it has a radically different structure (i.e., a series of nearly parallel straight-through holes). Whereas the methods of production are different, the flow pathways through [both] types of [media] are quite similar in terms of the tortuosity of the flow pathways."

Filters can be utilized with either personal sampling pumps or with stationary sampling devices. Filters for use in conjunction with personal sampling pumps typically are intended for flow rates of 0.5 to 4.0 L/minute, while flow rates as high as 40 or 50 ft^3/minute are typical for filters used in conjunction with high-volume air samplers (e.g., TSP, as specified in 40 CFR 50). As with the resin tube holders described above, filter holders are widely available, generally from the same manufacturers as the filters. For personal sampling pumps, 37-mm filter cassettes are widely used as sample medium holders (i.e., they are the standard accepted in the United States). As illustrated in Figure B8-5, filter cassettes typically consist of a three piece plastic ring "sandwich" in which the filter resides. These devices can be used open-faced (e.g., the actual diameter of the filter) or closed-faced (e.g., air flows through a 4-mm diameter orifice in the center of the cassette). Larger diameter, circular filters and cassettes of similar design are often used with rotary vane vacuum pumps for velocity considerations or trapping particulates. [Note: When used as an open-faced device, the third piece of the filter cassette is added

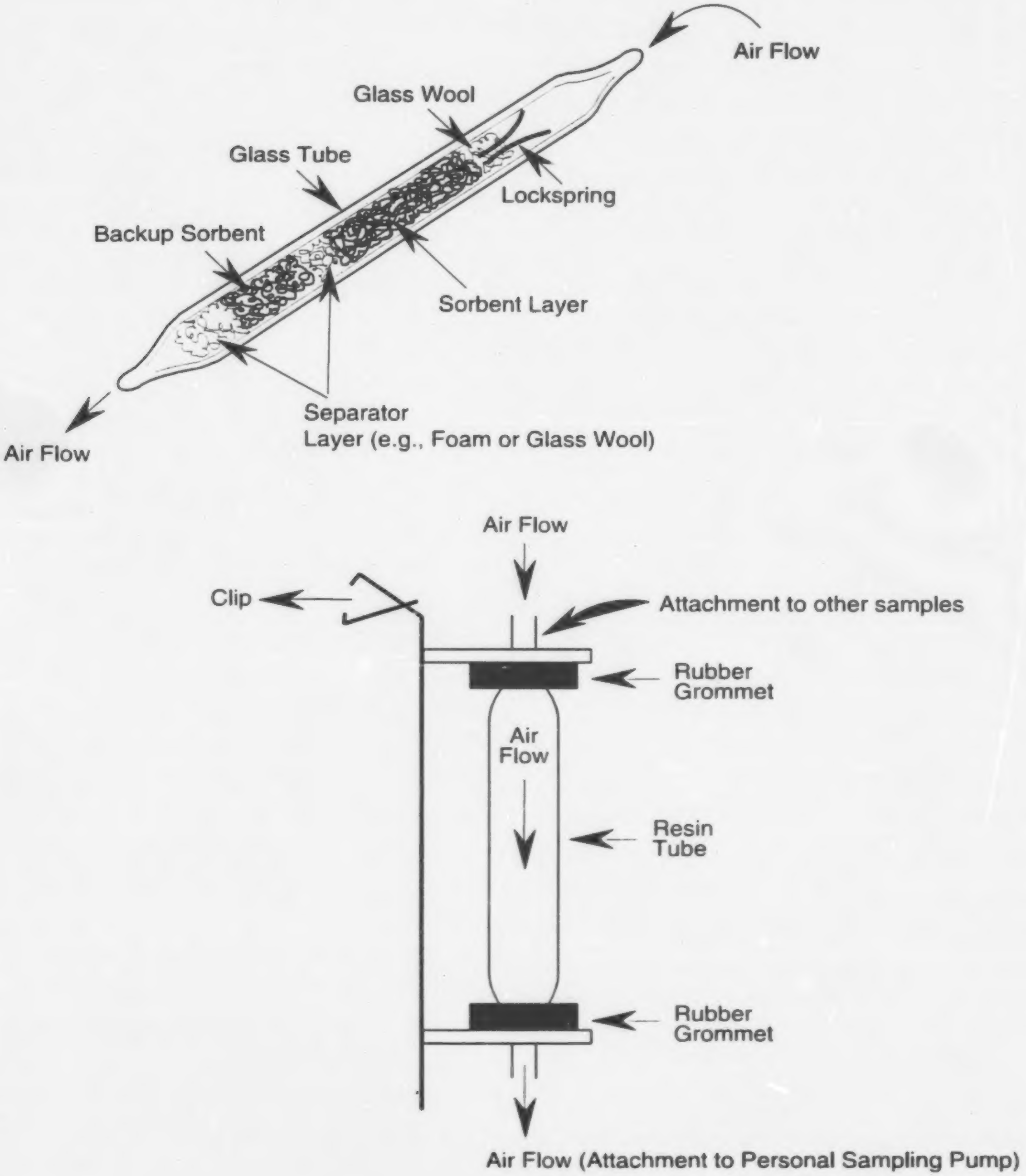
Air Flow
Glass Wool
Glass Tube
Lockspring
Backup Sorbent
Sorbent Layer
Separator
Layer (e.g., Foam or Glass Wool)
Air Flow
Air Flow
Clip
Attachment to other samples
Rubber
Grommet
Air
Flow
Resin
Tube
Rubber
Grommet
Air Flow (Attachment to Personal Sampling Pump)

Figure B8-4. Schematic of Typical Resin Tube/Holder

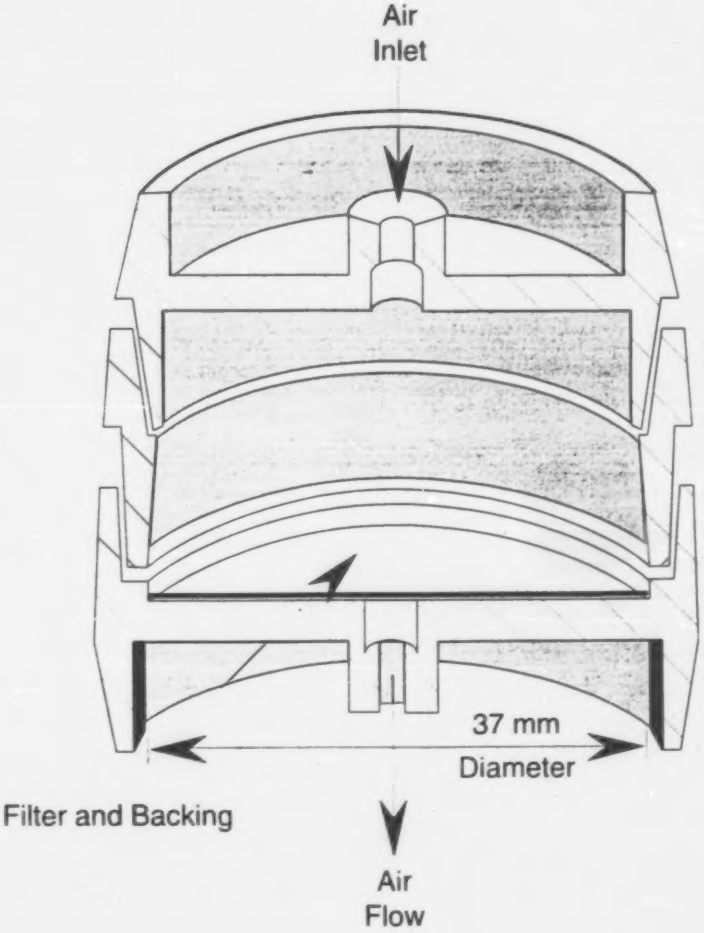
Air
Inlet
37 mm
Diameter
Filter and Backing
Air
Flow

Figure B8-5. Schematic of Typical 37 mm Filter Cassette

after sampling to seal the cassette and is not utilized during sampling.] Filters are usually attached to the high-volume air samplers using a device produced by the manufacturer which is specific to the device (e.g., rectangular filter cassette for TSP sampling).

Polyurethane Foam (PUF). PUF media are available in several physical configurations. Regardless of the configuration, PUF provides a medium through which ambient air is drawn (using either low flow personal monitoring pumps or high volume stationary sampling devices) to trap chemical residues in the gas, vapor, and/or the particulate phases. Cylindrical PUF plugs (e.g., 0.5-inch diameter x 1.5 inches long for personal sampling and 2.2 x 76 cm long for ambient air) are typically placed in some type of holder that can either be positioned in-line with other devices or used without a pre-filter. PUF used in stationary, high-volume air samplers is generally larger (e.g., 6 cm diameter plugs; ASTM, 1997b). These PUF filters are affixed to the samplers with a threaded or snap-on arrangement. For high-volume air samplers, sampling flow rates are generally in the 20 ft^3/minute range.

Particulate Sizing Devices. Inhalation of particle-bound chemical residues may result in a biologically effective dose even when inhaled particulates are too large to penetrate the lungs, due to absorption through the gastrointestinal tract (ACGIH, 1995). Therefore, in the majority of pesticide exposure scenarios, the Agency is interested in total airborne particulate levels rather than just the respirable fraction. The total airborne contaminant may be defined as airborne particles for which the aerodynamic diameter is < 100 μm (ACGIH, 1995). However, there are a limited number of postapplication scenarios (e.g., respirable particulate fractions of wind blown chemical laden soil particles or residue laden house dust) for which knowledge of the respirable particulate levels may be important. The respirable fraction of a contaminant may be defined as airborne particles for which the aerodynamic diameter is < 10 μm, although generalizations regarding the site of deposition of particles of a given size are problematic. However, in the average adult, most particles larger than 10 μm aerodynamic diameter are deposited in the nose or oral pharynx and cannot penetrate to tissues distal to the larynx, and the alveolar region has significant deposition efficiencies for particles smaller than 5 μm and larger than 0.003 μm (Casarett et al., 1995). Where exposure to respirable particulates is likely to be of toxicological significance, the Agency reserves the right to require that respirable particulate levels be measured .

The respirable particle fraction can be quantified using devices of two basic designs, the cyclone or the inertial impactor. (See Figures B8-6 and B8-7.) Both devices operate on the principles of momentum and force. In cyclones, airborne particulates are drawn into a cylinder where the air is flowing in a circular pattern. As the entrapped particulates move around the cylinder in a circular motion, the lighter, respirable particles are carried to the outlet and are collected on a filter contained in

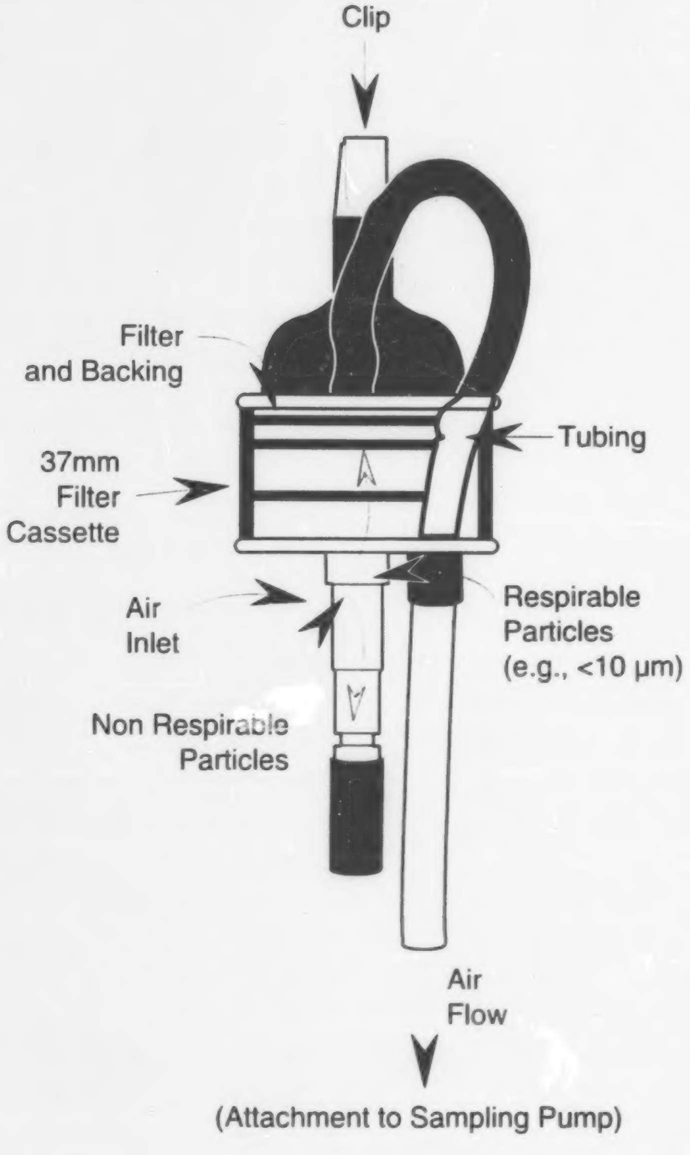
Clip
Filter and Backing
Tubing
37mm Filter Cassette
Air Inlet
Respirable Particles (e.g., <10 μm)
Non Respirable Particles
Air Flow
(Attachment to Sampling Pump)

Figure B8-6. Schematic of Typical Cyclone Device

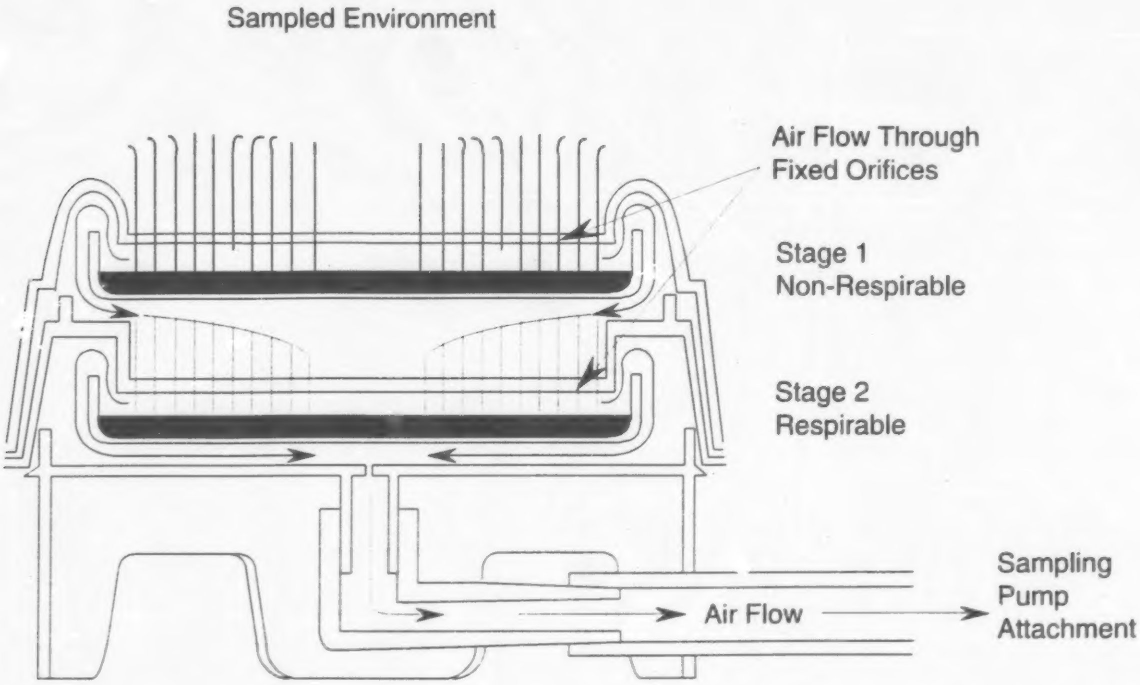
Sampled Environment
Air Flow Through
Fixed Orifices
Stage 1
Non-Respirable
Stage 2
Respirable
Air Flow
Sampling
Pump
Attachment

Figure B8-7. Schematic of a Typical Inertial Impactor

a typical 37-mm cassette. (See Figure B8-6.) The heavier particles are retained in the cylinder and are discarded. Size separation is now often also achieved using inertial impactors. In these devices, air is drawn through a series of orifices that limit particle sizes in sequentially smaller fractions as illustrated in Figure B8-7. Inspirable aerosol samplers are also available that are based on the concept of inertial impaction (Vincent and Mark, 1987).

Trapping Solutions (e.g., impingers and diffusers). Trapping solutions are used in conjunction with impingers or diffusers to entrap airborne chemical residues in various phases (e.g., gas, typically a gas or vapor, potentially particulates) during either personal or area monitoring. Impingers are suited for monitoring aerosols and other airborne particulates, while diffusers are better for quantifying gases, vapor phase contaminants, aerosols, or liquids. The design of both types of devices is similar. Essentially, both devices consist of a graduated cylinder (e.g., ~25 mL volume) outfitted with an air sampler attachment orifice and a ground-glass or threaded stopper through which a tube runs from the ambient air down into the trapping solution. (See Figure B8-8.) In both types of devices, sampled air is drawn through the tube directly into the trapping solution. As the sampled air exits the end of the tube into the solution, bubbles are formed by the vacuum placed on the device by the attached sampling pump. The design of the end of the tube which is placed in the trapping solutions differentiates the two types of devices. In impingers, an open-ended tube is placed directly in the trapping solution so that the tube end is at a fixed distance from the bottom of the flask. (See Figure B8-8.) As a result, airborne particulates can pass through the tube and are trapped in solution. Impingers may also trap gases or vapors. However, impingers may not as efficiently collect gases that have a low reactivity with the trapping solution. Diffusers are suited for monitoring only gases, vapors, and aerosols (e.g., liquid particulates). The design of a diffuser is intended to absorb or collect gaseous contaminants. A fritted glass diffuser head may be attached to the end of the tube that is immersed in the trapping solution. As air passes through the diffuser head, the total surface area of the bubbles created is much larger, thus, enhancing the probability that a gas or vapor may be absorbed into the trapping solution. The total surface area is larger for diffusers because larger numbers of smaller bubbles are created due to the number of orifices in the diffuser head in comparison to the single immersed tube that is characteristic of an impinger. Typically, individual orifices in diffuser heads are extremely small in diameter, thus, inhibiting the passage of particulate materials into the trapping solution. A variety of trapping solutions can be used with impingers and diffusers. Selection of the appropriate trapping solution depends upon the physical/chemical characteristics of the analyte. Commonly used solutions include, but are not limited to, the following: ethylene glycol, weak acid/base solutions, common organic solvents (e.g., hexane, xylene and acetonitrile), and various buffer solutions. For most monitoring purposes, the use of impingers/diffusers is appropriate only for personal monitoring in conjunction with personal sampling pumps operating at flow rates of 0.5 to 2.0 L/minute. Impingers/diffusers are typically filled to

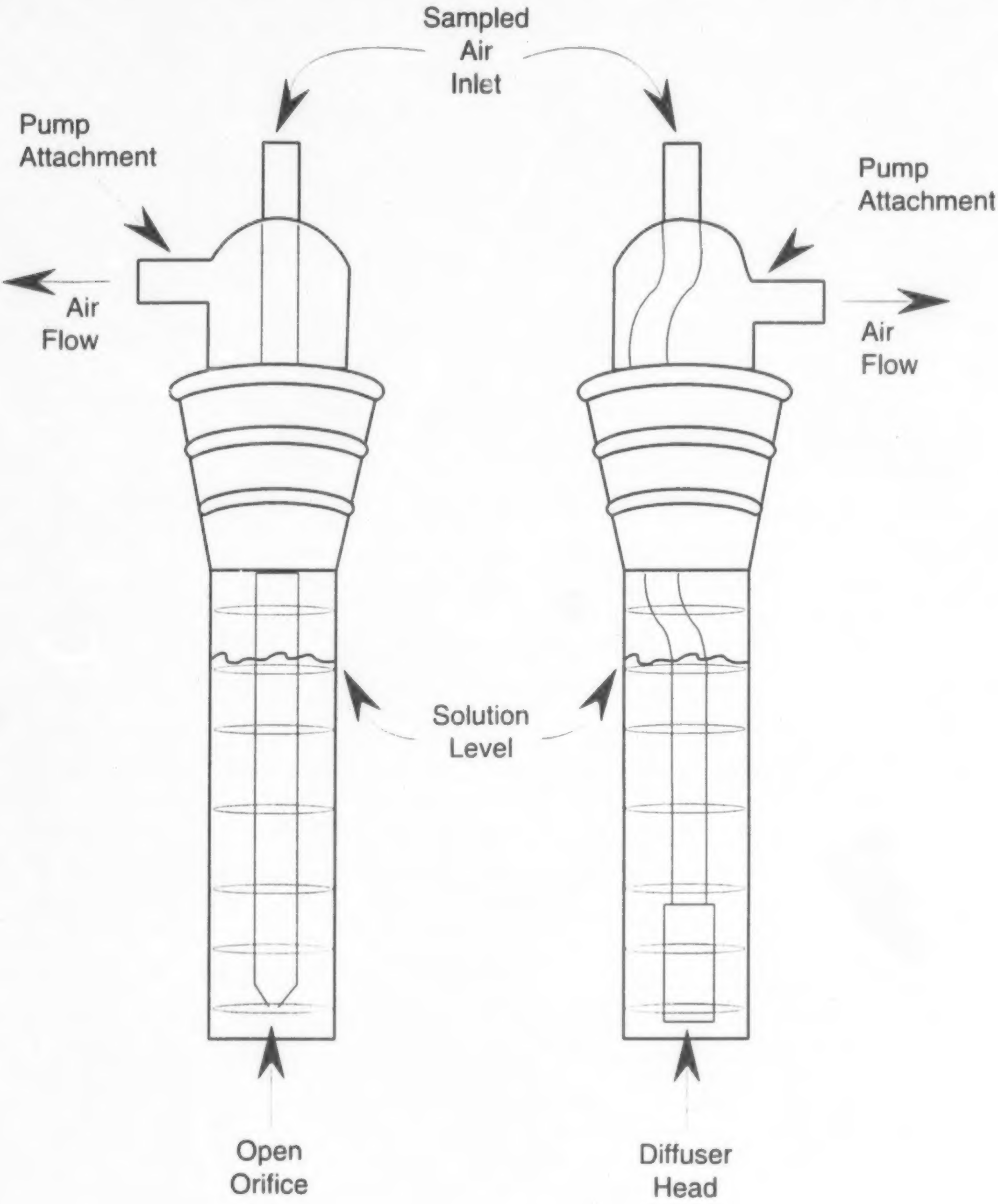
Sampled
Air
Inlet
Pump
Attachment
Pump
Attachment
Air
Flow
Air
Flow
Solution
Level
Open
Orifice
Diffuser
Head

Figure B8-8. Schematic of a Typical Impinger and Diffuser

approximately 80 percent of their total volume during sampling to ensure that the sampled air will bubble through a sufficient volume of trapping solution.

8.2.6.5 *Small Scale Environmental Chambers*

Small environmental test chambers are often used to evaluate and characterize the emission of organic compounds, under controlled conditions, from a variety of materials and products into indoor air. The source emissions data from these studies can be used to predict indoor air concentrations of the compounds emitted from the tested material, and subsequently to estimate inhalation exposure. The standard exposure chamber for evaluation of emissions is typically constructed of a nonabsorbent, chemically-inert, smooth interior substance, most commonly glass or stainless steel, so that the emitting substance does not adsorb to or react with the interior surface of the exposure chamber. Studies using glass or stainless steel environmental test chambers have been typically carried out for three reasons (Sollinger and Levsen, 1993): (1) to identify parameters which influence the rate of chemical emissions from a given source; (2) to rapidly screen materials used indoors in order to determine the emission potential; and (3) to simulate as closely as possible real indoor conditions thus allowing the estimation of the contribution of the emission of a given product to the total indoor air concentrations. Once a generation rate (G) for a given material is determined, it can be used in indoor air models to predict indoor air concentrations. This generation rate could be a function of time, concentration, or other parameters. Small environmental test chambers are designed to permit testing of various types of building materials and consumer products. They typically range in size from a few liters to 5 m^3. Chambers greater than 5 m^3 are considered large (ASTM, 1990). The standard exposure chamber has an access door with air-tight, non-absorbent seals, and is fitted with inlet and outlet ports for airflow. Currently, the ASTM standard (ASTM D5116-90) for small environmental chamber testing advises that the test chambers be designed to ensure (1) adequate mixing of the chamber air, (2) the air velocity around the tested material is not excessive, and (3) temperature, relative humidity, and light are appropriately controlled.

The limitations of current small scale chamber designs include the following:

(1) They cannot be used to directly measure the airborne concentration of an off-gassed material that can be expected in an indoor environment. Chambers with nonabsorbent surfaces may give erroneous and unrealistically high results relative to actual concentrations of some compounds found in the indoor environment. The actual concentration will depend on the amount of product applied or the material loading ratio, as well as effects of indoor sinks; and

(2) They should not be used to measure generation rates (G) when there is evidence that degradation of the compound of interest takes place on the walls of the chamber. In

those situations, erroneously low results relative to actual source rates will be measured.

A true maximum emission rate (Gmax) for a given product or material may be determined by measuring the amount of active ingredient in the air, and possibly on the walls of the chamber, during the first few hours of the experiment. Comparison of total mass emitted over a longer period of measurement with mass applied, if known, will enable estimation of losses due to degration.

Several resources are available for the planning and conduct of small scale environmental chamber testing. These include, but are not limited to, the following: ASTM accessible on the Internet at http://www.astm.org; ASTM (1992); and ASTM (1996).

8.3 SAMPLE STORAGE

Samples should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis; more detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. The study investigator is responsible for demonstrating the stability of the samples under the storage duration and conditions used.

8.4 SAMPLE ANALYSIS

Appropriate cleanup procedures should be used and the pesticide residues quantified by the best available method. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

8.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating exposure and risk.

8.6 DATA PRESENTATION

Inhalation exposure residue data should be reported in tabular form. These data should be reported as total μg/sample and as an airborne concentration ($\mu g/m^3$). Additionally, all other sampling parameter data generated concurrently with the residue data must be reported (e.g., pump flow rates--Lpm, pump calibration data--Lpm before and after exposure replicate, and the duration of the exposure replicate--minutes). Distribution data should be provided, to the extent possible.

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PART B - CHAPTER 9
NONDIETARY INGESTION EXPOSURE ASSESSMENT

9.1 INTRODUCTION

This Guideline provides a description of the methods and computational factors that may be used to assess postapplication nondietary ingestion exposure to pesticides. Nondietary ingestion exposure may occur as a result of: (1) inadvertent ingestion of soil that contains pesticide residues; (2) ingestion of pesticide-treated foliage, pesticide granules/pellets (e.g., used to treat residential lawns) or pesticide-laden paint chips; and (3) hand-to-mouth or object-to-mouth transfer of pesticide residues that have accumulated on the hands or objects that have come in contact with pesticide residues on indoor surfaces such as carpet, countertops, or hard flooring or on lawns or other outdoor surfaces, e.g., soil. The nondietary ingestion route may be particularly important for infants and children exposed to lawn chemicals and household pesticide products in residential settings because of the incidence of hand-to-mouth activity (Hawley, 1985) or object-to-mouth activity (Reed et al., 1997) and the activities performed by children (e.g., crawling) that put them in close proximity with treated surfaces (U.S. EPA, 1998a; 1998b). Children described (American Academy of Pediatrics, 1990; Bredekamp, 1985; U.S. EPA, 1998a) as crawlers and walkers (ages 8 to 18 months) and toddlers and two-year olds (18 months to three years of age), spend a substantial portion of their time indoors. A child's greater surface area to body weight might make increased dermal exposure more hazardous (Wolff and Schecter, 1991; Snodgrass, 1992). Nondietary ingestion exposure may be estimated using residue data for the media of interest (i.e., turf, soil, indoor surfaces) and standard ingestion rates, based on the age group or activity of interest. Assessment of nondietary ingestion exposure requires compliance with various other Guidelines presented in Series 875, Group B (i.e., Part B, Chapters: 4 Transferable Residue Dissipation: Lawn and Turf; 5 - Soil Residue Dissipation; and 6 - Indoor Surface Residue Dissipation.

9.2 SAMPLE COLLECTION

9.2.1 Test Substance

The test substance to be used for nondietary postapplication exposure assessments must be a typical end-use product. Where metabolites or breakdown components of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling on a case-by-case basis.

9.2.2 Timing of Application

Testing should be conducted during the intended use season. If outdoors, weather forecasts should be studied, as much as possible, to avoid initiating testing immediately (e.g., within 24 hours) before a precipitation event.

9.2.3 Pesticide Application Rate and Frequency

Generally, the typical end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower rate. For example, typical rates are often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will provide additional information about the relationship between the application rate and the residues available for nondietary ingestion. Also testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

9.2.4 Sampling and Assessment Parameters

Sampling parameters should be based on the following criteria:

- Residue deposition and dissipation data should be collected from the types of surface media associated with the typical use of the product. If the product is used indoors, then the surface media might be carpet, vinyl and wood flooring, and/or sheetrock (U.S. EPA, 1998c). If the product is used outdoors, then the surface media might be lawn, soil, and/or foliage. Registrants should discuss with EPA the surface media to be sampled during protocol development.

- Residue deposition and dissipation data for the media of interest should be collected from at least three environmentally distinct locations of varying temperature and relative humidity per formulation type (U.S. EPA, 1998c). Refer to the appropriate chapters for guidance concerning the types and numbers of samples that are appropriate.

- The sampling period should be of long enough duration and sampling intervals within the sampling period should be selected to adequately characterize dissipation. For dissipation sampling, at least three replicate samples should be collected from representative sampling environments at each sampling interval. See Part B, Chapters 4, 5, and 6 for additional information on sampling requirements.

- Highly exposed (or sensitive) populations should be evaluated (e.g., ingested dose among children is higher than for adults because of the higher rates of soil ingestion) (U.S. EPA, 1996).

- As a high-end, acute estimate, postapplication exposures should be estimated for the day of application for residential scenarios. Subchronic or long term exposures should be assessed using dissipation data for the media of interest.

9.2.5 Sampling Techniques

The selection of a sampling method will depend on the nondietary pathway(s) of interest. Investigators should consider all potential pathways of nondietary ingestion exposure (e.g., soil ingestion plus hand-to-mouth transfer and object-to-mouth transfer of surface residues) that are applicable,

9.2.5.1 *Inadvertent Soil or Dust Ingestion*

Soil or dust may be ingested by children and adults as a result of normal mouthing behaviors. Incidental soil or dust ingestion may be associated with activities such as children playing on treated areas (i.e., yards or playgrounds, or in indoor settings) or adults performing gardening activities in treated areas. Inadvertent soil ingestion exposure may be assessed using soil or dust residue data and standard soil or dust ingestion rates for various age groups [i.e., the product of soil or dust residue concentration (mg/g) and soil or dust ingestion rate (mg/day) yields potential dose (mg/day) from nondietary soil or dust ingestion]. See Part D, Chapter 2 - Calculations for more information on the calculations required for estimating exposure from incidental soil ingestion. Soil should be collected and analyzed for soil pesticide residues based on the guidance provided in Part B, Chapter 5 - Soil Residue Dissipation (Guideline 875.2200). Dust may be collected and analyzed based on guidance provided in Part B, Chapter 6 - Indoor Surface Residue Dissipation. Soil and dust ingestion rates should be based on the recommended age-specific values provided in U.S. EPA (1996). Additional guidance for assessing nondietary soil ingestion exposure is provided in U.S. EPA (1998a).

9.2.5.2 *Ingestion of Pesticide-Treated Foliage*

Pesticide-treated foliage may be ingested by toddlers playing on treated residential turf or playgrounds as a result of mouthing behaviors. Exposure to pesticides from nondietary ingestion of pesticide-treated foliage may be assessed using dislodgeable foliar residue data and estimates of the amount of foliage that children may be likely to ingest while playing outdoors [i.e., the product of dislodgeable foliar residue concentration (mg/g) and foliage ingestion rate (mg/day) yields potential dose (mg/day) from nondietary ingestion of treated foliage]. See Part D, Chapter 2 - Calculations for more information on the calculations required for estimating exposure from incidental ingestion of treated foliage. Treated foliage should be collected and analyzed for dislodgeable residues based on the guidance provided in Part B, Chapter 4 - Transferable Residue Dissipation: Lawn and Turf (Guideline 875.2100). Ingestion rates for foliage should be based on the weight of the estimated area of turf ingested, as provided in U.S. EPA (1997).

9.2.5.3 *Ingestion of Pesticide Granules/Pellets, or Paint Chips*

Dry pesticide materials in the form of granules/pellets, or paint chips may be ingested by toddlers who play in pesticide-treated areas (i.e., yards, gardens, playgrounds, or home treated with pesticide-containing paints). Exposure from inadvertent ingestion of pesticide granules/pellets may be assessed using the fraction of pesticide active ingredient in the granules/pellets and a standard ingestion rate [i.e., the product of the fraction of active ingredient in the dry pesticide formulation and the ingestion rate of granules/pellets (mg/day) yields potential dose (mg/day) from ingestion of dry formulation]. Ingestion exposure for paint chips may be assessed using information on the percent of active ingredient in the paint, and a standard ingestion rate for paint chips. Studies to evaluate the dissipation of pesticide active ingredients in dry pesticide formulations and paint should be proposed to the Agency in the study protocol, on a case-by-case basis. See Part B, Chapter 2 for the factors that should be considered when designing a residue dissipation study. See Part D, Chapter 2 - Calculations for more information on the calculations required for estimating exposure from ingestion of granules/pellets, or paint chips. Additional guidance for assessing nondietary ingestion exposure from pesticide granules/pellets and paint chips is provided in U.S. EPA (1997).

9.2.5.4 *Hand-to-Mouth Transfer*

Pesticide residues may be transferred to the skin during postapplication contact with treated indoor (i.e., carpet or hard surfaces such as floors or countertops) or outdoor areas (i.e., turf or foliage). Nondietary ingestion exposure from hand-to-mouth transfer and object-to-mouth transfer may be assessed using transferable residue data for the surface area of the hands of children and standard assumptions regarding the frequency of hand-to-mouth and object-to-mouth activity. The mass of residues ingested may be calculated for various age groups as the product of the transferable residue concentration (mg/cm^2), frequency of hand-to-mouth or object-to-mouth activity (events/day), and surface area contacted from which residues are ingested (cm^2/event) to yield potential dose (mg/day) from hand-to-mouth transfer See Part D, Chapter 2 - for more information on the calculations required for estimating exposure from hand-to-mouth transfer. Depending on the scenario of interest (i.e., indoor or outdoor) dislodgeable residues should be assessed based on the guidance provided in Part B, Chapter 4 - Transferable Residue Dissipation: Lawn and Turf (Guideline 875.2100) or Part B, Chapter 6 - Indoor Surface Residue Dissipation (Guideline 875.2300). The frequency of hand-to-mouth activity may be based on data in U.S. EPA) (1998a) and data on surface areas of the hands for specific age groups may be based on data from U.S. EPA (1996). Additional guidance for assessing nondietary ingestion exposure from hand-to-mouth transfer is provided in U.S. EPA (1998a).

Recently, EPA's National Exposure Research Laboratory (NERL), Human Exposure and Atmospheric Sciences Division (HEASD) designed a program to explore the pediatric and behavioral science literature for activities such as hand-to-mouth or object-to-mouth activity that could be used to explain nondietary exposures (U.S. EPA, 1998a). Statistical prior or "premodel" distributions of activities were to be established based on demographic characteristics. These premodel distributions were to be tested in field studies at day care centers where the behavior of children could be both observed directly by experts and videotaped. These studies would be expected to produce a data base of "postmodel" distributions for certain patterns of behavior that could be studied under controlled laboratory conditions using adult human subjects to measure dermal contact and transfer of surface residues by whole-body dosimetry. The aim of the research was to reduce or eliminate the need for exposure studies that require human subject participation. U.S. EPA (1998a) summarized data taken from the open literature on the duration and extent of hand-to-mouth and object-to-mouth activity, sorted according to predictor variables. The predictor variables included factors such as age, sex, ethnicity, and socioeconomic status. The literature review demonstrated the relative importance of the factors impacting nondietary ingestion exposure. These data may be useful for assessing nondietary exposure from hand-to-mouth or object-to-mouth activity for the population of interest.

9.3 SAMPLE STORAGE

In general samples should be stored in a manner that will minimize deterioration and loss of analyte between collection and analysis. Sample storage techniques should be consistent with the guidance provided for the media of interest (i.e., soil, indoor residues, foliar residues etc.) for the nondietary ingestion scenario being evaluated, as described above. Detailed information on sample storage is provided in Part C, Quality Assurance and Quality Control. The study investigator is responsible for demonstrating stability of the samples under the storage duration and conditions used.

9.4 SAMPLE ANALYSIS

Appropriate cleanup procedures should be used and the pesticide residues quantified by the best available method for the media of interest. See Part C, Quality Assurance and Quality Control for more detailed information on sample analysis.

9.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating exposure and risk.

9.6 DATA PRESENTATION

Data on nondietary ingestion exposure should be presented as the mass (mg) of active ingredient per day, or as an average daily dose or lifetime average daily dose (mg/kg/day), for the population(s) and exposure scenario(s) of interest.

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PART B - CHAPTER 10

BIOLOGICAL MONITORING

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PART B - CHAPTER 10
BIOLOGICAL MONITORING
GUIDELINE 875.2600

10.1 INTRODUCTION

Biological monitoring provides the basis for estimating an internal chemical dose by measuring pesticide and/or metabolite compound concentrations in selected tissues, fluids, or bodily wastes (feces and/or urine) (Woollen, 1993). The data generated using this guideline will serve as the basis for regulating chemicals in various settings, including agriculture, industry, and the residential market. This regulation will be based on the exposure and risk assessment process using the data. Additionally, this data can be used in conjunction with concurrently gathered ambient chemical dissipation data to establish total exposure transfer coefficients. These transfer coefficients can be used in the exposure and risk assessment process to predict exposures for specific activities using ambient concentration data in the absence of scenario-specific exposure data. Monitoring pesticide or metabolite levels associated with short biological half-lives (e.g., blood levels) may be an appropriate measure of current or very recent exposures; monitoring associated with long biological half-lives may be an appropriate measure of integrated exposure over an extended period of time (ACGIH, 1990). The most appropriate methods for biological monitoring should be chosen based on a thorough knowledge and understanding of the pharmacokinetics of the specific pesticide in humans, whether recent or long-term exposures are to be captured by the monitoring technique (Woollen, 1993; Chester, 1993).

In contrast to biological monitoring which measures the pesticide or its metabolites in human tissue, biological effects monitoring (i.e., use of biomarkers) has been used to detect evidence of chemical exposure by measuring a biochemical response, such as changes in enzyme activity (Chester, 1993). In other words, pesticide exposure is estimated based on an indicator property rather than through direct quantification of the chemical itself. This type of monitoring does not provide a direct measure of internal dose, but it can provide an indication of the potential for adverse effects. Dose cannot be estimated unless the correlation between exposure and biochemical response is well understood.

Biological effects monitoring has a long history of use in occupational settings. Correlations between levels of exposure to various industrial chemicals and covalent adducts between the chemical, or its metabolite, and hemoglobin have been reported (Tannenbaum and Skipper, 1984; Pereira and Chang, 1982; Popendorf, 1992). Specific examples of industrial chemicals for which this approach has proved useful include ethylene oxide (Calleman et al., 1978), chloroform (Pereira and Chang, 1982), and aniline (Neumann, 1984). One example of biological effects monitoring with regard to pesticides is the use of cholinesterase levels in the blood as an indicator of worker exposure to organophosphate pesticides (Peoples and Knaak, 1982; ACGIH, 1990). Attempts to correlate levels of cholinesterase inhibition with concentrations of pesticides and/or their metabolite/analog compounds in blood have been generally unsuccessful (Bradway et al., 1977, Roan et al., 1969, Drevenkar et al., 1983) because of the wide variability in cholinesterase levels among individuals (Popendorf and Leffingwell, 1982). Because biological effects monitoring does not yet provide quantitative estimates of pesticide exposure, the focus of this chapter is on biological monitoring of pesticides and their metabolites in human body tissues or body fluids.

Analyses of blood and urine are the most frequently used types of pesticide biological monitoring. Blood analysis is used to measure current or recent exposures. However, it is not as frequently used because of the invasive nature of the collection method. Urine analysis is used to measure the elimination of a pesticide and/or its metabolite/analog compounds as an indicator of exposure. The presence of the parent compound or known urinary metabolites has been used for almost four decades as an indicator of exposure to a number of pesticides including paraquat (Swan, 1969), arsenic (Gollop and Glass, 1979; Wagner and Weswig, 1974), parathion (Lieben et al., 1953), chlorobenzilate (Levy et al., 1981), the phenoxy acid herbicides (Kolmodin-Hedman et al., 1983), and organophosphate pesticides (Kutz and Strassman, 1977; ACGIH, 1990). In recent studies, Dong et al. (1996) used urine monitoring with a pharmacokinetic model to simulate doses of malathion in individuals exposed to aerial sprays, and Krieger at al. (1996) evaluated urinary clearance of disodium octaborate tetrahydrate used for flea control on carpets and furniture. Besides being used as an indicator of exposure, urinary metabolites have been used to confirm poisoning cases involving pesticides, including those involving organophosphates and carbamates (Davies et al., 1979). Such studies have noted the relationship of the pesticide(s) and/or metabolite/analog compounds in urine to exposure. However, more typically, no accurate quantification of exposure was able to be made from these data, partly because of a lack of adequate understanding of the pharmacokinetics of the pesticides. Therefore, it is emphasized that a thorough knowledge of the human metabolism and pharmacokinetics associated with the pesticide of interest is required for biological monitoring to be a useful technique for estimating dose. Pesticides and/or the metabolite/analog compounds may also be monitored through fecal analysis even though there is, by comparison, relatively little literature on this approach. Analysis of sweat as a biological monitoring medium for pesticides has some potential, but is severely limited by potential contamination from the skin of exposed workers. Breath analysis has some limited use for monitoring very recent exposures to volatile nonpolar pesticides, particularly some fumigants (Wilson, 1986). Based on methodological considerations and ease of use, the main focus in biological monitoring of pesticide exposure will be the elimination of pesticides in urine. Urine is an ideal sampling matrix because its collection is relatively simple and non-invasive.

NOTE: Additional information is available on biological monitoring in NIOSH 1984. NIOSH Manual of Analytical Methods. National Institute of Occupational Safety and Health, Cincinnati, Ohio.

The Agency does not routinely require submission of biological monitoring data. However, if a study investigator believes that the criteria for biological monitoring described below can be met for a particular pesticide and chooses to monitor worker exposure using biological monitoring, the Agency will evaluate the resulting data and, if judged to be adequate, will incorporate the results into the risk assessment process. If a study investigator decides to undertake a biological monitoring study, adequate pharmacokinetic data must exist to effectively interpret the data. Prior to initiating a biological monitoring study, the study investigator must receive Agency approval of the specific study protocol.

Biological monitoring studies may be considered and proposed by study investigators as an alternative to passive dosimetry at both outdoor and indoor sites if the first criterion below is satisfied. Biological monitoring studies may be required by the Agency for a specific pesticide when both criteria below are satisfied:

> Criterion 1 -- The pharmacokinetics of a pesticide and/or metabolite/analog compounds (i.e., whichever method is selected as an indicator of body burden or internal dose) in humans is understood well enough that a back-calculation to actual dose is possible.
>
> Criterion 2 -- Passive dosimetry techniques are determined not to be applicable for a particular exposure scenario (e.g., for extremely volatile pesticides such as some fumigants or prolonged immersion or saturation of the skin with a nonvolatile pesticide).

Pesticides that are rapidly absorbed and are neither sequestered or metabolized to a great extent are usually good candidates for biological monitoring (Ritter and Franklin, 1989). Also, pesticides for which a quantitative relationship between exposure and urinary metabolites can be established, are good candidates for biological monitoring (Ritter and Franklin, 1989). In contrast, pesticides may not be suitable for biological monitoring if they are extensively metabolized into a large number of metabolites (Chester, 1993) or if they are substantially retained in the skin. Also, biological monitoring should not be considered if the pharmacokinetics in humans are not well characterized.

10.2 SAMPLE COLLECTION

This section provides guidance on collecting samples from the sites of interest. Consult Part B, Chapter 2 - Study Design for information on points to be considered in choosing sample sites and Part C, Quality Control and Quality Assurance for details on ensuring the integrity of the submitted data.

10.2.1 Test Substance

As stated at 40 CFR 158.390, the test substance to be used for inhalation exposure measurements must be a typical end-use product. Where metabolites, breakdown components, or contaminants of pesticide end-use products pose a potential toxicological concern, investigators may need to consider sampling for them on a case-by-case basis.

10.2.2 Timing of Application

Sample collection should be conducted during the intended use season or under climatic conditions that are essentially identical to those encountered during the intended use season. Weather forecasts should be studied to avoid initiating the testing immediately (e.g., within 24 hours) before a precipitation event. For further information on climatological considerations, see Part B, Chapter 2 - Study Design.

10.2.3 Pesticide Application Rate and Frequency

Generally, the typical end-use product chosen for the study should be applied at the maximum rate specified on the label. In addition to applying the product at the maximum label rate, it is suggested that the product be applied using a lower application rate. For example, the typical rate is often used in cancer assessments (U.S. EPA, 1997). Monitoring at more than one rate will provide additional information about the relationship between the application and exposure levels. Also, testing at a lower rate may prove to be beneficial in the event that the data from use of the product at the maximum application rate results in an unacceptable risk.

Where multiple applications are recommended, the minimum time interval between applications should be used. Also, the potential accumulation of residues from multiple applications should be considered. The application method and equipment typical for the selected test substance should be used.

10.2.4 Sampling Parameters

- A sufficient number of replicates should be generated to address the exposure issues associated with each population of interest. In general, each study should include a minimum of 15 replicates per activity. Where possible, these replicates should be distributed as follows: 5 replicates (e.g., individuals) on each of three monitoring periods (e.g., "n" days after application). Investigators must be flexible concerning the number and distribution (e.g., locations and intervals after application) of the monitoring replicates. Because the aforementioned guideline cannot be expected to apply to all potential scenarios, the Agency requires investigators to submit protocols for review purposes prior to the inception of a study.

- The exposure monitoring period must be of sufficient duration, and the analytical method must have adequate sensitivity to ensure that each monitored activity has been sufficiently evaluated . Minimum sample volume and analytical quantification limits should be reflective of appropriate toxicology endpoints. (See Part C - QA/QC for a discussion of determining appropriate limits of quantification). The activity must be well defined and be representative of typical practice. Most postapplication activities range from 4 hours (e.g., harvesting roses/chrysanthemums in a greenhouse) to 8 hours (e.g., harvesting strawberries). Thus, a representative monitoring duration based on typical activities is recommended for each replicate. Justifications for determining monitoring durations should be provided in the study protocol.

- Biological monitoring must be carried out concurrently with transferable residue studies. Refer to the appropriate chapters for guidance concerning the types and numbers of transferable residue samples that are appropriate

- The selected sites and seasonal timing of monitoring must be appropriate to the activity. The need for studies under different geographical/climatological conditions should be considered.

- If biological monitoring is conducted concurrently with passive dosimetry, consideration should be given during the study design phase to ensure that the methods used for one monitoring technique do not invalidate the other (e.g., multiple handwashes during a monitoring period may reduce the amount of pesticide residues available for absorption or multiple layers of clothing).

- Monitoring should be conducted before residues have dissipated beyond the limit of quantification.

10.2.5 Sampling Techniques

The biological monitoring techniques described in this Guideline include measurement of pesticides and their metabolites in blood and urine. Although the Agency accepts both techniques, urine is the preferred method because it is relatively easy to collect, is non-invasive, and is biokinetically more stable. The proposed method for biological monitoring should be presented to the Agency for review in the study protocol for approval prior to commencing work on the study.

10.2.5.1 Blood

Because prior exposures to some pesticides may have a significant impact on blood levels, baseline blood samples should be taken from each individual prior to exposure. A brief history should be taken from each participant relating to known prior exposures to pesticides for at least the last 2 weeks, including reentry into potentially treated fields (ACGIH, 1990).

Sampling of pesticides or their metabolites in blood should be conducted in a manner that accounts for the considerations summarized in Table 10-1. Blood may be sampled using venous blood or capillary blood from fingers or ear lobes, except under the restriction that capillary blood is not an acceptable media when more than 0.5 mL of blood is needed for an adequate method sensitivity (i.e., to obtain a quantification limit that is low enough to be meaningful), when the chemical to be analyzed is present at the location where the samples are collected (because of the risk of external contamination), or when a specimen is being analyzed for volatile chemicals (because of loss by evaporation) (ACGIH, 1990). Venous blood should be collected in sealed containers. For volatile pesticides or metabolites, special procedures may be required to minimize the headspace in sample containers into which pesticides can be lost. If headspace exists in the sample containers in which volatile pesticide residues are collected, it must be analyzed separately from the blood.

For each 10 mL of unclotted blood, the sample container should contain one of the following anticoagulants designated as appropriate by consultation with the laboratory: 20 mg of potassium oxalate or sodium oxalate, 50 mg of sodium citrate, 15 mg of disodium-EDTA, or 2 mg of heparin. The potential for the anticoagulant interacting with the analytes of interest must be considered in selecting an appropriate anticoagulant. The anticoagulant of choice should have been dispersed along the bottom wall of the tube and then dried. Immediately after sample collection, the sample tube should be rotated gently to thoroughly mix the blood with the anticoagulant. A variety of blood collection devices are commercially available. Investigators should be careful to adhere to the manufacturers' guidelines and protocols when using the equipment (e.g., vacutainer tubes). The potential for the analyte of interest to adsorb to syringes and collection tubes must also be considered.

Table 10-1. Methodological Issues in Sampling, Storage, and Analysis of Blood, and Urine

Issue	Blood	Urine
SAMPLING		
Suitable determinants	Any	Any (although most convenient for polar determinants)
Specimen characteristics	Whole blood, plasma, serum, cells, clotted blood	Timed specimen
Invasiveness	Invasive	Noninvasive
Collection period	Instantaneous	Short-term (24 hours to several days)
Special qualification of health personnel	Medical staff required to obtain sample	Minimal training required
Infection protection	Sterile needle	Clean container
Container requirements	Anticoagulant	Wide Mouth
	Made of material that does not react or absorb determinant	
Volume	Depends on method	50 mL or more aliquot taken from a 24-hour sample
Precautions	Proper timing of sample collection required	
	Venus blood preferred (versus capillary blood, which is only appropriate in limited cases); proper anticoagulant; dry syringe	Sample only persons with normal renal function
Potential sources of contamination	Skin exposure, cleaning solutions, syringe, needle, anticoagulant	Cross contamination from exposed hands, hair, clothing (sampling after shower and clean clothes preferred)
Health hazards	Hepatitis, HIV[a]	Minimal[b]
TRANSPORTATION AND STORAGE		
Potential sources of contamination	Container	
Source of deterioration	Hemolysis, bacterial decomposition, light	Bacterial decomposition, light
Other transport issues	Low temperature required	Large volume and weight of samples
Storage temperature	Refrigerated or frozen (after separation of serum and plasma)	Refrigerated or frozen

Table 10-1. Methodological Issues in Sampling, Storage, and Analysis of Blood, and Urine (continued)

Issue	Blood	Urine
ANALYTICAL		
Cleanup procedure	Complex	Some
Possible interferences	Protein binding, conjugation, and chelation (impact dependent on analytical method)	
Method	Sensitive and specific	
DETERMINANTS REQUIRING SPECIAL CONSIDERATIONS		
Parent chemical	Avoid contamination during sampling procedure	
Volatile chemicals	Use airtight containers with controlled head space	

[a] Personnel involved in the collection and handling of human blood are subject to the provisions of OSHA regulation of Bloodborne Pathogens 29 CFR 1910.1030.

[b] While urine does not normally contain blood and is therefore not explicitly covered by OSHA regulation of Bloodborne Pathogens 29 CFR 1910.1030, protective measures are suggested by the potential for blood cells to be in urine due to various disease entities in participants.

Source: ACGIH 1990.

In addition, a number of precautions should be taken relating to blood monitoring: (1) medical staff should take appropriate precautions to protect both the study participants and staff from exposure to infectious agents (such as HIV); (2) samples should not be drawn from body parts that are known to be contaminated (e.g., from a spill onto skin); (3) prior to drawing blood, the collection site (e.g., arm, finger) should be washed with either detergent and water or isopropyl alcohol and dried; (4) appropriate precautions should be taken so that other chemicals do not contaminate the sample; (5) during analysis, samples should be well mixed prior to removing an aliquot for analysis to avoid errors because of sedimentation; and (6) analyses should account for the fact that some determinants can be present in free, conjugated, and protein-bound forms (samples analyzed for total determinant may require appropriate acid or enzymatic hydrolysis prior to analysis) (ACGIH, 1990).

10.2.5.2 Urine

Prior exposures to the test pesticide or structurally related compounds may interfere with the results of urine sampling for a biological monitoring study. Thus, a sufficient time period between such exposures and participation in the study is required to ensure adequate urinary clearance of the compound and its metabolites, based on pharmacokinetic data.

Sampling of pesticides and/or their metabolite/analog compounds in urine should be conducted in a manner that accounts for the considerations summarized in Table 10-1. Urine collection should cover 24-hour periods. Collections should begin on the day before participating in the postapplication exposure monitoring activities and continue on the day of postapplication monitoring and for an appropriate time period after these activities have been completed, depending on the excretion kinetics of the compound. The 24-hour collection cycle should begin with the first void after beginning work activities and end with the first void on the following morning, continuing this 24-hour cycle on subsequent days. All urine specimens collected should be logged in at the time of collection. The subjects sampled should be provided with readily sealable containers (i.e., that prevent spillage) of approximately 500 mL volume for every 6 hours or a larger container for collecting urine over the entire 24-hour period. These should be prerinsed with an appropriate solvent, or heated to 250°C (if glass) for 1 to 2 hours to prevent contamination.

The material used in the construction of the collection bottle should not interfere with (e.g., absorb) the analytes of interest. Materials may include polypropylene or polyethylene collection vessels and caps or glass bottles. Inert materials such as polytetrafluoroethylene (PTFE) should be used for caps. Special precautions are needed for specimens collected for measurement of volatile chemicals. If a large container of known volume is used, the laboratory must sample and analyze both the liquid and its head space. In either case, samples must be collected in containers that can be immediately sealed and kept airtight, and the containers should be able to withstand the pressure changes caused by changes in temperature during transportation and storage. Another consideration in selecting appropriate collection vessels is the light sensitivity of the analyte (i.e., amber bottles can be used if the analytes are degraded by light). Based on the stability of the analyte of interest at field temperatures, urine samples may be refrigerated or other methods of cooling may be used to preserve the integrity of the samples. Preservatives should be added as needed if they do not interfere with measuring the analyte.

After collection of a 24-hour urine sample has been completed, the urine volume should be measured and two aliquots of 50 mL or more should be taken and stored depending on the requirements of the analytical method. One sample may be transported to the analytical facility for analysis while the other set remains in local frozen storage at least until the first set has arrived at its destination at the laboratory. The considerations for selecting appropriate storage containers are the same as those described for sample collection containers.

10.3 SAMPLE STORAGE

Once the field samples have been collected, the next step is to transport the samples to the analytical laboratory and store them until analysis. Samples should be transported on either wet or dry ice, as appropriate, to minimize analyte dissipation. After arrival at the analytical laboratory, samples should be stored as noted below. Because of the diverse nature and properties of potential biological monitoring indicators, some analytes may exhibit unusual behavior under these storage and transport guidelines. If investigators deviate from the aforementioned guidelines because of the unusual physical/chemical characteristics of the analyte(s) of interest, the rationale must be documented in any submission to the Agency.

If biological monitoring media are to be stored after exposure, a stability test for the analyte(s) of interest should be documented in conformance with the medium-specific storage precautions noted below. See Part C, QA/QC for more information regarding procedures for initiating a stability study. In short, fortified media must be stored under the same conditions that will be used for field samples. In addition, the storage stability samples are to be handled and analyzed by the same methods that will be employed for field samples.

10.3.1 Blood

All blood samples should be treated with a minimum of agitation and temperature changes during transportation and storage to minimize the extent of hemolysis (ACGIH, 1990). If the analysis is to be done on separated serum, the collected venous blood should be allowed to clot in collection containers that are not treated with anticoagulant. The clot is then removed about 10 minutes after collection, and the serum is withdrawn by syringe (ACGIH, 1990). Whole blood samples should never be frozen; for overnight storage, refrigeration at 4°C is usually satisfactory. For longer storage, samples should be centrifuged, and the plasma should be removed for storage. Field blanks and other appropriate control samples (e.g., field fortifications) should be included in the analysis (ACGIH, 1990).

10.3.2 Urine

All urine specimens should be stored frozen after the specific gravity is measured.

10.4 SAMPLE ANALYSIS

The selection of analytical procedures will depend on the particular chemical or metabolite being studied. Consequently, this decision is left to the discretion of the investigator.

Urine samples collected over a 24-hour period should be well mixed before aliquots are taken for chemical analyses. The investigator should determine creatinine levels as a way of qualitatively monitoring completeness of urine collection samples. Corrections to adjust urinary residue levels in incomplete samples on the basis of urinary creatinine levels have limited utility because of the wide intra- and inter-individual variability of creatinine output (Alessio et al., 1985; Boeniger et al., 1993). Therefore, the quantitative use of creatine as a basis for adjusting urinary chemical residue output is discouraged by the Agency. Creatinine may be measured using a colorimetric method known as the Jaffe Reaction (Boeniger et al., 1993). Specific gravity, as another measure of 24-hour sample completeness (Alessio et al., 1983), can be read using a densitometer; this analysis should be performed as soon after collection as possible (and before sample storage) before irreversible sedimentation of solids occurs in the samples. Most clinical laboratories can perform these two analyses at relatively low cost. Specimens showing physiologically impossible low levels of creatinine or specific gravity should be viewed as having been tampered with and should be either discarded or reported with an appropriate footnote.

10.5 CALCULATIONS

Refer to Part D of this document for a description of the calculations needed for estimating exposure and risk.

10.6 DATA PRESENTATION

The amount of chemical should be reported for each sample and as a cumulative total for each exposure period. Residue data should be reported electronically in tabular form (i.e., spreadsheets). Distributional data should be provided, to the extent possible.

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PART B - CHAPTER 11

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PART B - CHAPTER 11
PRODUCT USE INFORMATION
GUIDELINE 875.2700

11.1 INTRODUCTION

To more accurately assess pesticide exposure, the Agency needs good information on how the pesticide under review is actually used and applied in the field or around the home. EPA also needs information on the types of activities individuals perform in pesticide-treated areas. This latter data requirement is described in Part B, Chapter 12 - Descriptions of Human Activity.

11.2 DATA REQUIREMENT

The types of use data that the Agency is requesting are detailed below. In the absence of precise data, ranges or estimates are acceptable if a supporting rationale is provided. The investigator should indicate sources of estimates and the relative reliability or accuracy of estimates. Trends in use or other relevant data which can enhance or clarify the Agency's understanding of the use estimates should also be provided. Use data are considered product specific, and are required of all registrants; a generic data exemption is not applicable.

11.2.1 Agricultural Scenarios

For agricultural-use pesticides, the following information should be provided, as appropriate.

Major use sites. The major use sites to which the pesticide under investigation is applied should be listed. Information on the size of these major use sites should also be provided. Generally, use sites for agricultural scenarios will be field crops. If the pesticide is used regionally, the areas where it is used should be listed.

Cropping systems. How the crop is cultivated should be discussed. For example, are the crops staked (e.g., tomatoes may be staked or allowed to grow on the ground), what systems are used for weed control (plastic, hoeing), etc.? If different cropping systems are used in various regions, these systems should be described.

Pesticide application. The typical application method, rates (pounds per acre), number of applications per growing season, and application interval should be described. This type of information allows the Agency to determine if the application pattern will be affected by a particular restricted-entry interval.

Reentry information. See Part B, Chapter 12 - Descriptions of Human Activity.

11.2.2 Industrial Scenarios

For industrial-use pesticides, the following information should be provided, as appropriate.

Major use sites. Industrial use sites generally will involve antimicrobial pesticides. Antimicrobials may be used as preservatives and incorporated during the manufacture of goods and articles (e.g., paper, paints, plastics, leather, etc.). Antimicrobials also are used in aqueous systems to prevent the growth of microorganisms (e.g., cooling towers, slurries, pulp and papermill water systems, metalworking fluids, etc.). The types of use sites to which the pesticide under investigation is applied should be listed. Most industrial uses will be nonfood-use sites.

Pesticide application. The typical application method (e.g., pump, pour, closed system, metered pump), rates, application frequency, and application interval should be provided.

Occupational activities. See Part B, Chapter 12 - Descriptions of Human Activity.

11.2.3 Residential Scenarios

For residential-use pesticides, the following information should be provided, as appropriate. If there are regional distinctions within these factors, they should be described.

Major use sites. The types of use sites to which the pesticide under investigation is applied should be listed. For indoor residential uses, this would generally be non-food sites. For outdoor residential sites, use sites would typically be application to lawns and home gardens. If the pesticide is used regionally, the areas in which it is used should be listed.

Pesticide application. The typical application method (e.g., broadcast, band, spot spray), rates, application frequency, and application interval should be provided. For example, is the pesticide applied directly from the apparatus it is purchased in? Does it need to be mixed before use? What is the product formulation?

Residential activities. See Part B, Chapter 12 - Descriptions of Human Activity.

11.3 DATA PRESENTATION

The use information may be reported in narrative form. Where practical, tabular format should be used.

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PART B - CHAPTER 12
DESCRIPTIONS OF HUMAN ACTIVITY
GUIDELINE 875.2800

12.1 INTRODUCTION

Human activities play a crucial role in the nature and magnitude of exposure to pesticides. For example, in agriculture, the type of crop and the type of work performed has an impact on exposure. Human activity data provide information concerning the way humans are exposed to the pesticide being evaluated. Information on human activity patterns is important in understanding the potential routes and pathways of exposure. Activity data such as the frequency and duration of exposure are needed for the exposure calculations. These data are also useful for evaluating potential differences in exposures between different subpopulations (i.e., adults and children) and for determining how specific activity patterns affect exposure levels. Also, it is human activity that links the transferable residue data to dermal exposure data via the transfer coefficient. The Agency also needs data on how the pesticide under investigation is used and applied. This latter data requirement is described in Part B, Chapter 11 - Product Use Information.

12.2 DATA REQUIREMENT

Study investigators should prepare a brief description that includes the following items associated with the pesticide being studied:

Nature of human activity. The types of human activities associated with use of the pesticide need to be described. For agricultural situations, this would be a description of the reentry activities that are performed after pesticide application such as harvesting, thinning, scouting, etc. For residential situations, such activities would include children playing on pesticide-treated lawns and indoor surfaces (e.g., carpet). For industrial scenarios, this would be a description of the activities after application of the pesticide in a manufacturing process or to the aqueous system being treated.

Principal source(s) of exposure. Pesticide exposures may occur from various sources. For agricultural scenarios, sources could include foliage, soil, and air; for residential scenarios, sources of exposure could include lawn, carpets, air, and counter tops.

Conditions mitigating exposure. For industrial pesticide uses, a description of any occupational safety and health regulatory and other requirements that directly mitigate potential exposures should be described. This may include mandatory air exchanges, engineering controls, air concentration exposure limits (permissible exposure limits PELs), short-term exposure limits (STELs), threshold limit values (TLVs)), personal protective equipment requirements, etc.

Level of physical exertion. Postapplication activities involve mild, moderate, and heavy forms of exertion. Such information is particularly important in biological monitoring studies as exertion levels may effect the metabolism of the pesticide under investigation.

Expected frequency and duration of activity. The frequency and duration of certain activities would impact exposure in accordance with the pattern of use of a pesticide product. In a residential environment, exposure would be dependent on the label uses and the frequency of ues in association with the duration and frequency of residential activities. The frequency of pesticide use, the number of hours worked per day, and number of days worked per year are all inputs into exposure/dose risk calculations that should be well documented by investigators.

Exposed Populations. The populations most likely to be exposed should be identified. For example, are adults or children, or males or females most likely to be exposed?

Unusual conditions contributing to exposure. Unusual conditions that might contribute to unforeseen and unpredictably heightened exposure should be considered. Are there specific conditions that may contribute to exposure during postapplication activities?

Efficiency of individuals conducting tasks. The act of performing human activities such as fruit or vegetable harvesting would be expected to contribute to exposure to pesticide residues through the transfer of residues from treated foliage to the skin. The efficiency of these operations would be expected to enhance exposure. For example, certain individuals might conform with or exceed the typical number of pounds of a commodity (e.g., fruits or vegetables) harvested on a daily basis. Such information will provide the Agency with insight on the intensity of the activity level associated with postapplication exposures.

Experience. The efficiency of the execution of an activity such as harvesting might be expected to depend on the experience of the individual. What is the typical experience level of individuals performing the task, using the product, and using any special or personal protective equipment? Also, how are experience levels likely to affect exposures?

EPA recommends that investigators document, in as complete a fashion as possible, the postapplication activities under which individuals may be exposed to the pesticide of interest via photographic and or videotape records (U.S. EPA, 1998a). These records should be retained with the raw data in archives unless specifically required by the Agency.

In connection with the submittal of descriptions of human activities, the study investigator should state which activity is the most likely to result in maximum human exposure to pesticide residues for each site. In some pesticide use situations, the most significant human exposure to pesticide residues occurs when harvested commodities are transferred from the application site and handled (e.g., sorting of fruits and vegetables). The study investigator should include a brief rationale supporting the selection.

12.3 ACTIVITY PATTERN (TIME USE) DATA SOURCES

An individual's choice of time use will vary according to parameters such as personal preference, age, gender, culture, hobbies, occupation, location, etc. Socioeconomic status and education attainment may also influence chosen activities and time spent. Activity pattern information and activity related exposure monitoring tools can be found in, but not limited to, the data sources that are briefly described below.

Exposure Factors Handbook - The Handbook, an EPA, Office of Research and Development (ORD) publication, presents information from various published time use/activity patterns surveys for adults and children in the U.S. general population and various subpopulations. The data included are for type of activity, time spent engaging in an activity, location of an activity, and number of times an individual may perform or engage in an activity. In addition, a description of each survey is provided (i.e., study design, study population, response rate, etc.). Activity Patterns Survey data are aggregated based on age, gender, race, geographic location, specific activity, etc. These data may be used to develop exposure duration and frequency estimates for specific exposure scenarios. (U.S. EPA, 1996a).

National Human Activity Patterns Survey (NHAPS) - NHAPS, an EPA/ORD effort, is the largest and most current human activity patterns survey and is representative of the U.S. general population. Data are available for 91 activities and for 82 different possible locations. Information was collected via 24-hour diaries on duration and frequency of selected activities and of time spent in selected microenvironments. Statistical summaries were generated for specific subgroups of the U.S. population (i.e., gender, age, race, employment status, education, census region, season, etc.). Data are reported in the form of means, percentages of time spent, and percentage of respondent occurrences. These data are useful for obtaining national representative distributions of time spent in a large variety of activities and locations in a single day. (U.S. EPA, 1996b).

National Human Exposure Assessment Survey (NHEXAS) - NHEXAS, scheduled to be completed in FY 97, is a Federal interagency program to measure exposure using estimates of frequency and durations of exposure-related human activities and data on pollutant concentrations in environmental and biological media. Among the target chemicals in the survey are pesticides. Human time-activity patterns information was collected and estimated using questionnaires and diary data. In addition, there are several special studies conducted that address activity or behavioral patterns: measurement and analysis of children's exposures to pesticides and PAHs (a feasibility study to evaluate total pesticide exposure and incorporate reported and observed activity patterns of children); quantification of children's hand and mouthing activities through a videotaping methodology (a videotaping methodology to quantify children's activity patterns by totaling the frequency and occurrence of behaviors of interest); and the Region 5 NHEXAS time/activity diary (a daily time-activity diary completed over a 7-day period). (Sexton et al., 1995; Quackenboss et al., 1997; Reed et al., 1997; Freeman et al., 1997).

ADP Information Resources Management and Support Services (AIRMS) Time-Location Methodology - AIRMS is in support of an EPA/ORD initiative to study incidental exposure of children in residential environments. It provides an analysis of available literature data on children's behavioral patterns: hand-to-mouth activity, object-to-mouth activities, locomotor activities, pica and geophagia, and other miscellaneous exploratory behaviors. The report is a summary of the statistical analysis of prediction (age, sex, ethnicity, socioeconomic status, etc.) and response (drop or bang objects, touch or grasp object, look at object, mouthing object) variables. Frequency and duration data are available for selected activities. (U.S. EPA, 1998b).

Consolidated Human Activity Database (CHAD) - CHAD was developed to support exposure/intake dose/risk assessment for the EPA Office of Research and Development. CHAD is a relational data base with graphical user interface that facilitates queries and report generation. It contains data bases from existing human activity patterns surveys (questionnaire or diary data) that are either national in scope or are site-limited. These data bases have been incorporated into CHAD as the original raw data and as data modified to format requirements. The graphical user interface design includes button and pull-down menus for customizing queries and a user may access personal diary information (age, gender, ethnicity, education and activity, and other questionnaire information) for each survey respondent. Queries can be made of the original survey data or the modified CHAD data, and a user can select a single variable (e.g., respondent's age) and apply it to all studies contained in CHAD. Interpretation of the variable (e.g., activity codes) is identical for all studies in CHAD for the modified data, but not for the original survey data. (U.S. EPA, 1997).

Jazzercize TM - Exposure Monitoring Tool - Jazzercize TM, as an activity-related exposure monitoring tool, was purposefully designed to achieve maximum contact of the entire body with the floor using low impact aerobic movements. Jazzercize TM is exercise that has been choreographed to music. Because the body motions are described on paper and timed to the beat of the music, Jazzercize TM is a very reproducible means of establishing the same extent of body contact with a treated surface anywhere a certified instructor can be found. Every surface of the human body (dorsal, ventral, and lateral) contacts the floor multiple times in a series of exercises which are timed to the nearest second. Repetitive movements are standardized by executing them to the beat of popular jazz music. Four stretching exercises are interspersed with four aerobic movement exercises. Test subjects wearing whole body dosimeters are lead through a prescribed set of exercises on a carpet or lawn previously treated with a pesticide. Immediately following the exercise, the dosimeters are collected, extracted, and analyzed to determine the amount of chemical transferred from treated surface to the dosimetry clothing.

In order to relate the degree of contact in this standardized exposure monitoring test to normal adult or children's behavior, one must know the kinesiology of both the test method (e.g., Jazzercize) and normal human behavior. The number of contacts various body parts make with a carpet, the intensity and duration of normal contact must be compared to the test method. Several studies have recorded activity patterns and, more recently, studies on children's behavior have better defined their kinesiology. However, at this time, no study has related the test method estimates of exposure to exposures measured following normal use. (Ross et al., 1990).

In a recent study, Krieger et al. (1996) used the Jazzercize TM method to evaluate exposure to disodium octaborate tetrahydrate, on indoor flea control pesticide used on carpets. Study participants performed a 20-minute set of Jazzercize TM routines on treated carpet. Exposure was measured using whole body dosimeters and biological monitoring (i.e., urine). The availability of pesticide on the carpet was evaluated using the California Cloth Roller as a sampler (see Part B, Chapter 6 - Indoor Surface Residue Dissipation for a description of this technique).

Time-Motion Videoanalysis - Recently, EPA has been conducting research using videotape analysis to determine how and to what extent humans, particularly biologically sensitive individuals, such as children, are exposed via the dermal route to pesticides used in residential microenvironments (U.S. EPA, 1997b). To accomplish this goal, video recordings were made of adult volunteers performing prescribed and choreographed activities of children (crawler/walker stage 8-18 months of age) reentering a pesticide treated room. Contact and transfer of residues were examined to obtain passive dosimetric data in conjunction with time-motion analysis of the videotapes. The study examined the concordance of exposure duration, anatomical areas exposed, and skin surface area exposed with direct measurement of contact by passive dosimetry. Duration of exposure, as determined by time-motion analysis of activities within a microenvironment, was found to correlate with dosimetric measurements of the anatomical regions of the body in contact with contaminated surfaces. As part of this research, a videotape analytical technology was identified that converted video images into reproducible and quantitative computer data using digital systems instead of analog systems. This technology, the Peak Performance Technologies Motion Measurement System (PPT-

MMS) was able to capture activities at the level of detail important to EPA to make informed judgements about location of contact, anatomical area of contact, duration of contact, and the activity associated with exposure. The PPT-MMS provided a quantitative and reproducible method for the measurement of the biomechanics of exposure that may be adaptable to the modeling of exposures under a variety of scenarios. This "ergonomic approach" would enable the risk assessor/modeler to determine the exposure potential associated with individual activities in relation to surface area of contact and anatomical area of contact.

EPA's purpose in studying the biomechanics of exposure in confined spaces (microenvironments) is to reduce or eliminate the need for exposure studies that require human participation. The studies were designed to generate a computer assisted scenario-based model that can interpret spatial and temporal relationships of human dermal contact and transfer of surface residues. The initial studies were proposed to study dermal exposure and nondietary ingestion of toxic substances in children. The methodologies thus far developed could have wider applications to situations where humans may be occupationally exposed.

12.4 DATA PRESENTATION

Human activity information relevant to the pesticide being evaluated may be reported in narrative form. Where practical, tabular format should be used.

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PART C

QUALITY ASSURANCE/QUALITY CONTROL

PART C - QUALITY ASSURANCE/QUALITY CONTROL (QA/QC) C-1

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PART C - QUALITY ASSURANCE/QUALITY CONTROL (QA/QC)

1.0 INTRODUCTION AND OVERVIEW

The purpose of this chapter is to outline the quality assurance (QA) and quality control (QC) efforts required to support development of human exposure and dissipation data that are required under 40 CFR 158.390 and described in Part B of these Guidelines.

This Chapter is divided into five sections: (1) Introduction; (2) Pre-field Laboratory Considerations; (3) Field Study Considerations; (4) Laboratory Analysis of Collected Samples; and (5) Good Laboratory Practices (GLP).

The Pre-field Laboratory Considerations section covers those experiments associated with developing an analytical method for the analyte(s) of interest and validating its expected accuracy, precision, and specificity in a specific sample matrix. Requirements in this area include determining the laboratory recovery efficiency, limits of detection and quantification, and working concentration range of the method. Optional, but recommended, requirements include determining the stability of the samples under the expected conditions of storage as well as the recovery from fortified samples exposed under simulated field conditions.

The Field Study Considerations section covers the major aspects of proper sample collection and validation as specified in the study design. Sample collection requirements include, but are not limited to, calibrating application and sampling equipment, observing and documenting important aspects of study conduct, and ensuring that samples are properly handled and stored. Sample validation requirements include the selection of an appropriate control site(s) and the preparation and collection of field recovery samples.

The Laboratory Analysis of Collected Samples section covers the need for regular laboratory instrument maintenance and calibration programs, the use of standard calibration curves to correct for day-to-day instrument variability, and the preparation and analysis of concurrent laboratory recovery samples to verify that the losses during extraction, cleanup, analysis, etc. are within acceptable limits as defined by the pre-field method validation work.

The Good Laboratory Practices (GLP) section covers the procedures required by field and laboratory personnel to document the access, location, condition, and handling of each sample from the time of collection through analysis.

The Data Reporting section describes the treatment of nonquantifiable values, the presentation of field and laboratory recovery data, and the appropriate data calculation and correction procedures.

2.0 PRE-FIELD LABORATORY CONSIDERATIONS

Analytical methods and sample collection procedures should be developed and validated before the field monitoring portion of a study is undertaken. Many aspects of the overall study design, such as the nature of the active ingredient and the end-use product in question, the proposed sampling technique(s) and duration, the anticipated time and conditions of sample storage, etc. can influence the method development and validation process. Study design issues are discussed in Part B, Chapter 2 of these guidelines and should be considered for the study in question before and during method development and validation. In addition, the relevant toxicological endpoints (acute and chronic) for the compound in question should be considered during the method development and validation phase of the study so that acceptable margins of exposure can be demonstrated in the event that exposure samples yield values below the limit of detection (LOD)/limit of quantification (LOQ). Sufficiently low LOQ and LOD are expected so that the Agency can avoid having to estimate the margin of exposure (MOE). (See Part D, Chapters 1 and 2.)

Although it may be desirable to include a complete report of the method development and validation work in the protocol, it is not practical in most cases because this work may continue for several months subsequent to the completion of the protocol. However, as indicated in Part B, Chapter 2 - Study Design, the protocol should include a brief description of the anticipated analytical method to be employed and the proposed LOQ and LOD for each collection medium. The protocol should also include information on the stability of the analyte in or on the collection medium, if available. The final report of the study submitted to EPA must include a complete report of the method validation work.

2.1 Analytical Method Development

Analytical methods should be developed before field samples are collected. The method must be specific for the analyte of interest at an appropriate LOQ level. The necessary LOQ for any assessment will depend upon the toxicological endpoint of interest. At a very minimum, the LOQ must be sufficient to assess exposures below the no observable effect level (NOEL) based on the toxicological endpoint or its equivalent mg/kg for the appropriate dosing frequency, which may be daily. It is usually desirable and recommended to be able to quantify exposures well below the NOEL using a study design factor (i.e., historically referred to as a safety factor). One approach to estimate a LOQ for dermal exposures is to be able to quantify the NOEL delivered as a dermal dose deposited uniformly onto the 1.92 m^2 skin area (approximately 20,000 cm^2) of a standard 70 kg/person. The average dermal deposition density at this condition calculated by Equation C-1 reduces to approximately 3.5 NOEL ug/cm² for the standard person.

$$\text{Avg. Deposition Density, } \mu g/cm^2 = \frac{[\text{NOEL, mg/kg}] \times [\text{body mass, kg}] \times [10^3\ \mu g/mg]}{[\text{body surface area cm}^2]} \qquad \text{(Eq. C-1)}$$

A good target LOQ must be below the average deposition density presented in Equation C-1 because of: (1) the uncertainty in estimating a NOEL for the dermal route of exposure (e.g. the dermal NOEL may need to be estimated from oral NOEL times a coefficient representing the difference between dermal and gastrointestinal (GI) absorption); (2) differences between typical frequency and duration of use patterns and those actually assessed; (3) the reduction in collection time if assessments cannot be run for the full exposure period per day; (4) likely variations in chemical deposition densities over skin locations; (5) the potential impact of conservative interpretations of results below the LOQ (i.e., non-zero assumptions of nonquantifiable or nondetectable samples); and (6) uncertainties associated with toxicological endpoints such as inter- and intra-species variations. These study design factors (often described as a safety factor) do not add safety to the NOEL but encourage setting a target LOQ for dermal (or other field) exposure assessments that will be below the minimal concentration noted above by factors of 10, 100, or more.

$$\text{Dermal LOQ, } \mu g/cm^2 = \frac{[\text{dermal deposition density, } \mu g/cm^2]}{[\text{study design factor}]} \qquad \text{(Eq. C-2)}$$

Air sampling may or may not be targeted at the same NOEL, depending upon various factors such as differences in absorption rates or in metabolism between exposure via the air versus dermal routes. Estimates of a maximal LOQ for air samples can be calculated in basically two steps: first by calculating the airborne concentration corresponding to the most appropriate NOEL (Equation C-3), then by calculating the LOQ of the air sample's liquid extract (Equation C-4). As with the other maximal LOQ examples discussed herein, it is desirable to target an air sample LOQ below the maximal airborne LOQ by a study design factor of 10, 100, or more.

$$\text{Air Concentration, } \mu g/L = \frac{[\text{NOEL, mg/kg}] \times [\text{body mass, kg}] \times [10^3\ \mu g/mg]}{[\text{air volume inhaled during activity, L}]} \qquad \text{(Eq. C-3)}$$

Should a NOEL air concentration be available directly from some toxicity test, then only Equation C-4 need be used.

$$\text{Airborne LOQ, } \mu\text{g/L} = \frac{[\text{air concentration, } \mu\text{g/L}]}{[\text{study design factor}]} \qquad \text{(Eq. C-4)}$$

Two additional steps may be needed. Air volume sampled is determined by flow rate and time of the activity or the exposure being assessed. Keep in mind, the full duration of daily exposure may be different from the duration of time the air sample is actually collected, although as a first approximation they can be assumed to be equal.

$$\text{Air volume, L} = [\text{flow rate, Lpm}] \times [\text{sample collection time, minutes}] \qquad \text{(Eq. C-5)}$$

Should the toxicity data base yield a NOEL concentration in terms of ppm in the vapor state, a molar conversion must be calculated as shown in Equation C-6 based on the molecular weight of the analyte.

$$\text{Air Concentration, } \mu\text{g/L} = \frac{[\text{air concentration (ppm) x molecular weight}]}{[\text{24.45 L per mole at standard conditions}]} \qquad \text{(Eq. C-6)}$$

A similar approach can be applied to dislodgeable foliar residues (DFRs) by incorporating a transfer coefficient. A DFR corresponding to the NOEL can be estimated by first adjusting the dermal NOEL to some appropriate unit of activity, typically per hour, and then applying the corresponding transfer coefficient (e.g. Popendorf and Leffingwell, 1982). (See the discussion of transfer coefficients and alternative units of activity in Section D.2.5.)

$$\text{DFR at NOEL, } \mu\text{g/cm}^2 = \frac{[\text{NOEL, mg/kg}] \times [\text{body mass, kg}] \times [10^3\ \mu\text{g/mg}]}{[\text{work day, hr}] \times [\text{transfer coefficient, cm}^2\text{/hr}]} \qquad \text{(Eq. C-7)}$$

Finally, the LOQ to quantitate this DFR sample will depend upon the foliar sample collected and the design factor applied, as shown below:

$$\text{DFR LOQ, } \mu\text{g/cm}^2 = \frac{[\text{DFR at NOEL}]}{[\text{study design factor}]} \qquad \text{(Eq. C-8)}$$

Again, it may be desirable to target an LOQ for field studies to be below the above maximal DFR LOQ value by a study design factor of 10, 100, or more.

The procedures to estimate LOQs for biological monitoring are similar in principle to those described above, but the details vary with the biological index being assessed.

The analysis of urinary excretion is another laboratory problem similar to dosimetry except in an aqueous media. Quantitation requires an LOQ for the chemical/metabolite corresponding to the NOEL in the urinary volume over which the chemical/metabolite will be collected. In principle, there exists a consistent ratio between the mass of chemical exposure, the absorbed dose, and the amount of chemical or metabolite excreted. In reality, this ratio varies widely (ACGIH, 1990). Not only can the mass excreted per dose vary, but so can its rate of excretion and its concentration in the urine vary. Average urinary volume is 1.2 L/day (50 mL/hour), but this can easily vary ±3 fold and up to 4 or 5 fold under adverse circumstances of weather, fluid intake, metabolic and psychologic stress, medication, or disease.

For urinary monitoring to be a viable option, one must be able to anticipate either a proportionate amount of excretion over a given time frame following a single dose or a rate of excretion following a repeated daily dose. The first situation is applicable to rapidly metabolized chemicals; the latter, to more slowly metabolized chemicals. The general trend for pesticides is away from chemicals with long biological half lives, toward the more rapidly metabolized chemicals. Assuming that a ratio ($K_{excretion}$) can be defined between a predictable level (mg) of excreted chemical or metabolite at the NOEL (or ideally at any dose) as shown in Equation C-9, then the concentration that can be quantitated in the urine at this dose can be estimated from Equation C-10.

$$K_{excretion} = \frac{[\text{urinary excretion, mg}]}{[\text{NOEL, mg/kg}] \times [\text{body mass, kg}]} \qquad \text{(Eq. C-9)}$$

$$\text{NOEL, mg/kg} = \frac{[\text{urinary excretion, mg}]}{[K_{excretion}] \times [\text{body mass, kg}]} \qquad \text{(Eq. C-10)}$$

$$\text{Urine LOQ, } \mu\text{g/mL} = \frac{[K_{excretion}] \times [\text{NOEL, mg/kg}] \times [\text{body mass, kg}]}{[\text{study design factor}] \times [\text{urinary volume, L}]} \qquad \text{(Eq. C-11)}$$

This maximal LOQ can be greatly decreased if the chemical or metabolite in the urine is extracted and resuspended in another solvent, in which case this reduced extraction volume should be substituted for the urinary volume in Equation C-11. In addition to establishing a method with sufficient sensitivity, pre-field method development especially of a metabolite should also establish specificity from other natural or pharmacological sources. Collecting a pre-exposure sample from each individual (as discussed in Part B, Chapter 10) is a positive check on the adequacy of this aspect of pre-field method development, as well as the prior exposure status of participants.

The analysis of chemicals in blood can be treated in a manner identical to urine in Equations C-10 and C-11, if one can demonstrate or assume a similar ratio of blood content to dose exists for all dosing routes at equal points in time. It is desirable that the ratio between blood content and dose (k_{blood} in Equation C-12) be established for the most important environmental dosing route, although it is recognized that this toxicological data point is rarely available. The total blood volume used in Equation C-12 to derive k_{blood} would be the animal species tested; total blood volume in Equation C-13 would be for humans (which on average is 5 L but varies with weight, body build (fat-to-lean tissue ratio), and gender). Lacking any other measurable toxicologic parameter, any measured k_{blood} from a similar temporal dosing scheme could be used to establish a LOQ for blood at or below the NOEL using Equation C-13.

$$k_{blood} = \frac{[\text{blood concentration, } \mu g/L] \times [\text{total blood volume, L}]}{[\text{applied dose, mg/kg}] \times [\text{body mass, kg}] \times [10^3\ \mu g/mg]} \qquad \text{(Eq. C-12)}$$

$$\text{Blood LOQ, } \mu g/mL = \frac{[k_{blood}] \times [\text{NOEL, mg/kg}] \times [\text{body mass, kg}]}{[\text{study design factor}] \times [\text{total blood volume, L}]} \qquad \text{(Eq. C-13)}$$

2.2 Analytical Method Validation

Analytical method validation establishes the performance of a particular method (e.g., the expected accuracy, precision, and specificity of a procedure for specific concentration ranges) within an analytical environment (e.g., within the laboratory that will perform the analysis of field samples). Method validation includes the analysis of a range of recovery samples for each matrix, including the LOQ. Performance criteria should include a demonstration of the capability to attain reproducible results when measuring analytes at the desired level of sensitivity for all substrates prior to the initiation of field studies. Seven samples per fortification level per matrix are required for method validation experiments. The completion of all validation work prior to the initiation of field studies is not mandatory, but it is recommended. Method validation experiments must be conducted under GLP standards.

Minimally, the analytical method validation must include the following:

- Establishment of the method's working concentration range of expected values from the field studies.
- Determination of detector response over a reasonable standard concentration range.
- Determination of the accuracy and precision of the method within the analytical environment through an experiment that should include the analysis of at least seven replicates of each fortification level indicated below for each substrate:
  - The method limit of quantitation (LOQ),
  - An intermediate concentration level (e.g., 10X LOQ),
  - The maximum concentration of the validation range (e.g., 100-1000X LOQ), and
  - Blank or control substrate.

In most instances, an accuracy value between 70 and 120 percent (average recovery) and a precision value less than or equal to 20 percent (coefficient of variation) demonstrates the analytical environment's capability to perform accurate and precise analysis. Note: The analytical method's accuracy and precision can also be handled on a case-by-case basis.

2.3 Other Validation Studies

Storage Stability. A storage stability study can be conducted prior to or in conjunction with a field study. Its purpose is to determine the stability of analyte(s) in or on appropriate sample matrices under storage conditions similar to those anticipated for storage of field samples. Conducting a storage stability study prior to study initiation may eliminate the need for generating storage recovery data during the field conduct of the study.

A storage stability study should include the following parameters:

- Preparation and analysis of at least three blanks, three low-level fortifications (2-10X the LOQ), and three high-level fortifications in the expected range of the field samples for each storage interval, including the longest interval planned for storage of field samples; and
- Storage of stability samples under the same conditions of storage as planned for the field samples (e.g., sample matrices or extracts, ambient temperature and/or frozen, etc.)

A storage stability study, preliminary or in conjunction with the field study, is optional if the field QA/QC samples are stored and analyzed with the actual field samples.

Pre-Trial Field Recovery Study. A pre-field (simulated) field recovery study is optional but is recommended. The purpose of a simulated field recovery study is to estimate the potential loss of analyte from sample collection devices, when subjected to environmental conditions (e.g., temperature, light, relative humidity, wind) and sample durations representative of those anticipated during collection of the actual field exposure samples. Because a simulated field recovery study is optional and is intended only to further minimize the risk to investigators, the Agency will not request that a specific number of samples be completed. However, it is recommended that a simulated field recovery study consist of preparation and analysis of at least three blanks, three low-level fortifications (2-10X the LOQ), and three high-level fortifications in the expected range of field samples. Laboratory incubators can be used to simulate anticipated field temperature and humidity conditions. If environmental conditions are anticipated to change during the exposure monitoring period, then a worst-case scenario should be simulated. Investigators should consider worst-case scenarios by providing data pertaining to the physical/chemical characteristics of the pesticide(s) being studied and the anticipated climate where the study is to be conducted when simulating worse-case scenarios.

2.4 Sample Collection Devices

During the pre-field phase of the study, investigators must give consideration to selecting the most appropriate sample collection device(s) and methodologies available for monitoring the pesticide(s) and use scenario(s) in question. Dosimeters and other sample collection devices must be durable enough to survive the physical stress and duration of the overall monitoring effort, including sample collection, transportation, and analysis. In addition, reasonable judgement should be used in the selection of sample collection devices to ensure that they do not reach their absorptive capacity (i.e., become saturated) during the sample collection process. Sampling media should be selected that do not contain substances that might interfere with the analysis. Pre-extraction may be required to remove coextractants and contaminating substances. Also, investigators must consider logistics pertaining to the preparation and storage of any dosimeter and/or monitor.

3.0 FIELD STUDY CONSIDERATIONS

Proper quality control and quality assurance measures during the field phase of a study are critical for ensuring the protection of volunteer subjects as well as the scientific validity of the study. Field QA/QC considerations can generally be divided into three areas: those pertaining to the protection of study participants, those pertaining to analytical field operations, and those pertaining to field data collection and documentation. Only the latter two subject areas will be discussed here.

The protection of study participants is achieved through compliance with the provisions of the Worker Protection Standard and informed consent. (See Part B, Chapter 2 - Study Design.) Analytical field QA/QC operations are oriented toward quantitatively tracking the residue of concern throughout the field phase of a study (e.g., field recovery samples, optional travel recovery samples, fortifying procedures and the selection of a clean control site). Finally, critical elements for field data collection and documentation include: study site characteristics; application equipment and parameters; climatological data; sampling equipment and techniques; quality control and sample generation; dosimeter and sampler locations; human activity patterns; and sample storage and shipment.

3.1 Analytical Field QA/QC Operations

Analytical QA/QC considerations during the field trials of any study pertain to quantitatively tracking the residue of concern through the sample collection phase. The design of this aspect of the study is left to the discretion of the investigator as long as the stability of the compound is tracked from the field to the analytical phase. The most effective mechanism for completing this effort is through a properly executed field recovery regimen. Field recovery samples must be included in a study to allow the experimental data to be corrected for losses that occur during all phases of sample collection and analysis. Specifically, field recovery samples that are collected, handled, transported, and stored in conjunction with the experimental samples account for losses that occur during all phases of sample collection, sample handling and storage in the field, transportation from the field to the laboratory, and storage in the laboratory. Additionally, field recovery samples that are analyzed concurrently with the experimental samples account for residue losses that occur during sample extraction and analysis. Travel recovery samples can also be prepared in the field and shipped and stored with the experimental samples. The results of the travel recovery samples provide a basis for estimating the losses that occur during sample shipment and storage as opposed to those that occur during sample collection. The inclusion of travel recovery samples is optional.

3.1.1 Field Recovery of Human Exposure Samples

Field recovery refers to data generated to determine the loss of analyte from samples collected and fortified in the field, when subjected to the same environmental conditions (e.g., temperature, light, relative humidity, wind) and duration as field samples. Field recovery samples may also reflect the total losses that occur during sample collection, shipment, storage, and analysis.

Ideally, a separate set of field recovery samples should be collected for each work cycle (or activity period) monitored at each site. From a logistical standpoint, however, it is often more practical to collect one set of field recovery samples to represent all work cycles monitored at a given site on a given day. This approach is acceptable provided that the field recovery samples are collected in a manner that produces the most conservative estimates of recovery (e.g., collected during the highest temperature, wind, and/or relative humidity present during any of the work cycles monitored). It may also be acceptable to collect a single set of field recovery samples for all work cycles monitored at a given site over the course of a few days if the environmental conditions are similar each day. This approach is only recommended for compounds that are very stable and in locations where the climate does not change appreciably from one day to the next during monitoring. The investigator who chooses this approach to generating field recovery data must demonstrate the stability of the compound as well as the day-to-day consistency of the climate at the study site(s).

A complete set of field recovery samples are used to represent all workers monitored for each sampling matrix during a work cycle irrespective of their particular job function. In addition, the number of field recovery samples collected during a work cycle is not influenced by the number of workers being monitored. A complete set of field recoveries should consist of three or more each of blank control samples, low-level fortifications, and high-level fortifications. The low- and high-level fortifications should be in the range of the anticipated level of the chemical on the substrate. If the highest expected level is more than 100X the lowest fortification level, it is recommended that a mid-level of fortification be included.

It is advisable to generate sufficient field recovery samples to be analyzed with the actual field samples to serve as concurrent laboratory recovery samples. At a minimum, a complete set of field recoveries would consist of the following, as applicable.

Inhalation (air) Sampling Matrices. An appropriate number of controls, low-level fortifications, and high-level fortifications should be prepared and analyzed. The analyte should be added to the collection matrices in the field at the time of the study. After fortification and evaporation of the delivery solvent, the fortified matrices should be exposed to ambient conditions and attached to air pumps. The pumps should be operated in clean air at a flow rate, and for the length of time, equivalent to the field samples.

Patches. An appropriate number of controls, low-level fortifications, and high-level fortifications should be prepared and analyzed. The number of patches is irrespective of whether the worker wears 1 patch or 22 patches. However, if some patches are covered by clothing (inside patches versus outside patches), a separate set of fortified patches may be prepared and covered by clothing during the exposure period at the control site. If necessary, fortified outside patches can be substituted for fortified inside patches as they represent the worst case. However, this approach is not recommended as it can result in a considerable overestimation of losses during the sample collection period which, in turn, results in an overestimate of dermal exposure (outside patch field recovery used for inside patch correction).

Whole Body Dosimeters (WBDs). Preferably, investigators should collect field samples from test subjects in a manner that reflects the exposure to various regions of the body (e.g., field samples should be sectioned into samples of the following: arms, legs, front torso, back torso). A field quality control regimen should reflect this type of study protocol by using pieces of test garments for fortification as field recovery samples. Investigators must use discretion when preparing samples. For example, investigators could split a garment designated for QC purposes into samples that are reflective of the field samples (e.g., arms or legs) or into smaller fabric swatches (e.g., 100 cm^2) and fortify the individual samples. However, several issues must be considered when attempting to prepare such samples.

First, fortification levels must reflect the relative size of the QC fabric swatch samples as opposed to a typical sample (i.e., the fortification level should be similar to the anticipated field sample levels on a per area basis as analytical background may be important in the data interpretation). Second, the total solvent extraction volume should be proportional to the surface area for both the field exposure samples and the field recovery samples (e.g., if a solvent volume of 1,000 mL is used to extract a 2,000 cm^2 section of a field exposure sample, then a solvent volume of 50 mL should be used to extract a 100 cm^2 field recovery swatch). Third, QC sample swatches must be generated from the same production lots of dosimeters and prepared in the same manner (e.g., pre-extraction) as the monitors used to collect the actual field samples. Finally, the quantitation limit for each particular matrix must be considered when specifying fortification levels (e.g., the determination of low fortification levels when prorating based on the surface area of the sample). The use of fabric swatches will conserve considerable storage space and solvent usage. The similarity of recoveries should be established during method development and validation. If it is established that the fortifying of fabric swatches yields results similar to whole sections of the WBD, it is acceptable to use patches for field recovery samples.

Gloves, Socks, Undergarments, Head Bands, etc. Exposed clothing items, such as gloves (if used as a dosimeter), should be fortified at both the low level and the high level. Covered items, such as undergarments, may only need to be fortified at the low level, covered, and exposed to the elements at the control site.

Hand Rinses; Urine/Blood. It is not appropriate to expose hand rinse or biological samples to the environment during the field phase of a study because they are collected, processed, and stored immediately, without significant exposure to the elements. However, all samples should be handled using the same procedures as the actual field samples. For example, fortified hand rinse solutions should be "set out," for as long as it takes to conduct a hand wash (10-15 minutes), prior to storage or packing for shipment. If urine or blood is collected for biological monitoring, it is recommended that three samples of control (nonparticipant) urine or blood be fortified with two levels of the urinary analyte (parent or metabolite(s), whichever is appropriate) for each experimental site. These fortifications may be made just prior to going to the field, carried into the field during the course of a work cycle, exposed in a manner similar to participants' urine or blood, and stored and shipped with experimental samples. If stability of the analyte(s) has been rigorously established prior to study initiation, investigators may choose to reduce or eliminate this component from the study design because it is a burdensome task.

3.1.2 Field Recovery for Environmental Residues

This section describes how to generate field recovery data for any method designed to quantify transferable residues. Like the situation described above for hand rinses, dislodgeable foliar residue samples are collected, processed, and stored immediately without significant exposure to environmental elements. The objective of dislodgeable residue field recovery samples is to account for losses that occur from the time of collection through transportation, storage, and analysis. This can be accomplished by fortifying blank extract solutions at various sampling intervals and then transporting, storing (both in the field and in the laboratory), and analyzing the field recovery samples in conjunction with the foliar and soil residue samples. The blank extract solutions are prepared in the same manner as the dislodgeable foliar residue samples except that residue free foliage is used. On the other hand, residue free, sampling media, such as the PUF from the PUF roller, cloth from the Dow Drag Sled, or soil should be fortified directly. The recommended sampling intervals for dissipation studies are discussed in Part B, Chapter 2 - Study Design.

The frequency of preparing field recovery samples to correct for potential dislodgeable residue sample losses will be dictated by the stability of the pesticide in the extract solution as determined during the pre-field storage stability study. Pesticides that are relatively stable in the extract solution under the anticipated storage conditions will require that field recovery samples be prepared at less frequent sampling intervals than pesticides that are less stable. All foliar or soil residue samples collected in conjunction with or subsequent to each set of field recovery samples should be transported, stored, and analyzed concurrently with the field recovery samples. An alternative to analyzing the dislodgeable residue samples concurrently with the field recovery samples is to analyze them prior to the field recovery samples but in conjunction with concurrent laboratory recovery samples. A complete set of field recoveries should consist of at least one blank control sample and three or more each of a low-level fortification and a high-level fortification. The low- and high-level fortifications should be in the range of the anticipated levels of the residues in the field.

3.1.3 Travel Recoveries

Travel recoveries refer to experiments conducted to determine the stability of the analyte on each sampling matrix during shipment and possibly storage. Travel recoveries are optional and are left up to the discretion of the investigator. These recovery samples are prepared concurrently with the field portion of the study. They are then shipped and stored with the appropriate experimental samples. However, appropriate steps should be taken to ensure that commingling of these samples does not occur (i.e., travel recovery and field samples should be kept in separate containers within the shipping or storage unit to prevent cross contamination). The travel recovery samples are different than the field recovery samples in that they are not exposed to the environmental conditions during the sample collection period. Thus, the results of the travel recovery samples reflect losses that may occur during shipment and storage only as opposed to those that occur during sample collection, shipment and storage. It is suggested that one set of travel recovery samples be prepared for each experimental site to aid in the interpretation of losses that may occur in field recovery samples. If field recovery samples indicate no significant losses, the travel recoveries do not need to be analyzed.

3.1.4 Fortification Solutions

The importance of valid field recovery data (and thus, the ability to accurately fortify field recovery samples with a known mass of active ingredient) to the overall success of these studies cannot be overemphasized. It is recommended that a solution of the neat analyte, in the same form as applied, usually in an organic solvent, be used for fortifying all substrates. Such a solution is also recommended for fortifying hand rinse solutions and control urine samples, depending on the analyte. It is unlikely that the organic solvent used to prepare the fortifying solution will change extraction characteristics of the analyte because an extremely low volume of a concentrated solution is typically used to fortify samples. The concentration may have to be adjusted for fortifying at multiple levels. A description of the fortification procedures must be added to the final report.

3.1.5 Control Site

Blank samples and field recovery samples are to be prepared at a "control site" that is upwind and a reasonable distance from the treatment site to avoid potential contamination of the samples during application and/or postapplication activities. Good planning and adequate resources are required to have the control site established, and all fortified and control collection devices "running" while the field monitoring portion of the study is in progress. The exposure time at the control site should approximate the field sampling time as closely as possible.

3.2 Field Data Collection and Documentation

Comprehensive and accurately written and photographic field records are critical to evaluating the representativeness of a study's design and interpreting study results. As such, it is recommended that in addition to maintaining written documents as required by GLP, researchers photograph and/or videotape the various activities associated with sample collection (e.g., sample collection, sample storage, etc.).

The data collection requirements for the following phases of a field trial are described below.

- Study Site Characteristics;
- Application Equipment and Procedures;
- Climatological Data;
- Sampling Equipment and Techniques; and
- Exposure Activity Patterns.

3.2.1 Study Site Characteristics

A reasonable/general description (e.g., a diagram and/or text) of each study site (indoor and outdoor) must be included as part of the protocol and study report submitted to the Agency. Any equipment that is permanently situated onsite that might influence the exposure measurements must be described in the field notes, including such items as:

- Blocking and shade cloth arrangements in greenhouses;
- Ventilation systems; and
- Automated control systems (e.g., greenhouse climate, irrigation, etc.).

Soil must be characterized where applicable. Soil characterizations must include texture and classification.

3.2.2 Application Equipment and Procedures

Application procedures must be thoroughly documented. Sprayer calibration and formulated pesticide product samples as well as photographic records are essential in determining whether or not an application is valid. Valid application procedures are essential to any acceptable study.

All application equipment used in a study must be calibrated. Application rate verification (e.g., deposition coupon, calibration, inventory) is generally recommended and should be discussed with the Agency during the development of the study protocol.

Any equipment that is used during a study such as mechanized harvesting equipment, tractors, hand tools, and stationary packing equipment must be completely documented. This description should include the following characteristics:

- Equipment capacity (mechanical harvesters, cherry pickers, etc.);
- Attainable height (e.g., ladder height, cherry picker height, etc.);
- Equipment model and operating parameters;
- Hand tools (type, size, uses); and
- Picking site logistics and ergonomic factors.

3.2.3 Climatological Data

The following types of data are required, where appropriate, for dislodgeable foliar residue and soil residue dissipation studies (also, indoor studies, as appropriate):

- Air temperature (indoor also);
- Precipitation (natural and irrigation);
- Relative humidity (indoor also); and
- Air exchange should be described for indoor studies.

Study conditions and the physical/chemical properties of the pesticide(s) may require additional information be collected.

The Agency will note these data on a case-by-case basis.

The use of climate data from offsite sources is acceptable if large variances do not exist. Investigators must use their discretion when identifying sources of alternative data. For example, climatological data from weather station observatories near a study site can serve as an acceptable alternative for weather information monitored onsite if it can be determined that large variances do not exist between the climatic conditions at the two locations (e.g., spot check similarities at various intervals). Onsite monitoring of rainfall is recommended. If alternative data are used, a general discussion regarding why they were used must be included in the study report submission.

A relevant report of the effect of temperature and humidity on residue decay (and data reporting for that matter) may be found in Popendorf, W.J. and Leffingwell, J.T.: Natural Variations in the Decay and Oxidation of Parathion Foliar Residues. J. Ag. and Food Chem. 26(2):437-441, 1978.

3.2.4 Sampling Equipment and Techniques

A complete description of sampling techniques utilized by an investigator throughout the course of any study must be provided. The following types of information are required:

- Sampler make and model information; and
- Dosimeter design and attachment mechanisms.

Any sample collection equipment used in a study by an investigator must be validated and/or calibrated. Examples include: personal sampling pumps must be calibrated using a device that is traceable to or is a primary standard (e.g., bubble meter or "Buck-Type" calibrator); thermometers used in any study must be traceable to a National Institute of Standards and Technology (NIST) primary standard; and weights used to calibrate analytical balances must also be traceable to NIST primary standards. The validation/calibration should be described in standard operating procedures (SOPs).

A complete description of any sampling regimens utilized by an investigator throughout the course of any study must be completely described. The following types of information are required:

- Dosimeter location on each test subject;
- DFR Sampling regimen (e.g., Iwata Method for Trees); and
- Stationary Air Sampler Placement.

4.0 LABORATORY ANALYSIS OF COLLECTED SAMPLES

By the time the collected samples arrive at the laboratory, the study investigator should have a reliable analytical method in place. The basis for any modern analytical method is the specificity (e.g., separation). Instrumental methods that are both sensitive and stable should be developed. The analyte(s) of interest should be readily separated from the unidentified analytical response (UAR) by units of time, wavelength, etc., that are large enough to allow for accurate resolution and quantification of the analyte of interest. The lowest level analytical (i.e., calibration) standard should produce a signal that is at least three times greater in magnitude than the baseline background noise. In other words, the instrumental signal to noise ratio must be ≥3 for the lowest standard (Taylor, 1987).

4.1 Instrument Performance

Instrument performance must be monitored regularly to ensure the reliability of the measurements. Several techniques that can be used to establish instrument performance include, but are not limited to: (1) daily comparison of peak areas of analytical standards via linear regression, (2) calculation of a correlation coefficient for a particular standard curve, or (3) judicious selection of internal standards. Investigators must establish their own guidelines for determining whether an instrument is functioning properly, as this determination is dependent upon the analytical method, instrument operating parameters, and background levels observed and/or anticipated in the samples. Investigators should describe in detail any procedures used to monitor instrument performance on a routine basis.

Determining the proper instrument operational quality control procedures is difficult. Investigators must develop operational standards that are pertinent to the pesticide(s) being studied (e.g., detector response patterns affect calibration techniques). Investigators must also develop criteria for scrutinizing daily method performance data.

4.2 Calibration Techniques

Investigators should describe all techniques used to calibrate instruments and generate calibration curves. Data integration, besides enabling investigators to manipulate and interpret data in a variety of ways (i.e., various peak integration techniques), also typically generate calibration curves as well as calculate and summarize results. Several options for instrument calibration are usually available in each system (e.g., linear regression for all points, point to point calibration, average values based on multiple analysis, etc.). Investigators must be careful to consider the response patterns of a particular instrumental system (i.e., linear, exponential, threshold, etc.) prior to selecting a means to generate the calibration curve. Technique(s) employed by investigators to calibrate an instrument should be described in any submission to the Agency.

4.3 Concurrent Laboratory Recovery

Laboratory recovery samples are analyzed in the analytical laboratory concurrently with the field samples to confirm or determine the recovery efficiency of the analyte from substrates. Laboratory recovery samples are typically fortified with analytical standards or formulation and reflect losses that occur during laboratory operations (extraction, cleanup, analytical measurement, etc.). They are not intended to account for losses that occur during sample collection, shipping or storage. It is recommended that a minimum of ten percent of the field samples be represented by a laboratory recovery sample for each analytical batch or run. These laboratory recovery samples should cover the range of concentrations anticipated in field samples.

Laboratory recovery samples can be either fortified in the laboratory or in the field (i.e., field recovery samples). It is recommended, however, that the field fortified samples be used as concurrent laboratory samples, whenever possible. When used in this manner, the field fortified samples can be used to correct the field samples for both losses in the field and laboratory. However, if the investigator is not confident of the environmental fate of the compound in the field and during storage, samples generated in the laboratory should be used to identify where the losses may have occurred (i.e, field or analytical method).

5.0 GOOD LABORATORY PRACTICES

Quality assurance requirements may be found in the Good Laboratory Practice (GLP) Standards (40 CFR 160.35). These regulations "define the function of the quality assurance unit (QAU) in regulated studies as that of ensuring managers that all aspects of the facility, personnel, performance, recordkeeping, and reporting are consistent and in compliance with the regulations. The objective of the regulations is to ensure users...of (the generated) information...of accuracy and to ensure integrity of study conduct and reported results according to specifications in the GLPs."

Sample storage and shipment procedures as well as the chain-of-custody system must be documented in full. Any GLP exceptions need to be accepted by EPA in the protocol (e.g., container storage).

5.1 Sample Storage and Shipment

The study investigator should be responsible for demonstrating the stability of the samples under the storage duration and conditions used.

5.2 Chain-of-Custody

"Documentation of chain-of-custody is necessary to provide information concerning the handling of test substances, reference substances, control samples, and treated samples within the analytical laboratory. Chain-of-custody includes not only the receipt of a substance, but also from whom that substance was received and the condition of the sample upon receipt. Once a substance or sample is in the possession of the analytical laboratory, the storage conditions must be documented.

Chain-of-custody documentation provides a 'paper trail' that tracks the removal of these items from storage for any reason: weighing, mixing, spraying, sampling, processing, assay, or shipment" (Garner et al. 1992). Chain-of-custody is required under 40 CFR 160.81.

REFERENCES FOR PART C

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PART D

EXPOSURE AND RISK ASSESSMENT

PART D - CHAPTER 1

FUNDAMENTALS OF EXPOSURE AND RISK ASSESSMENT D1-1
1.1 INTRODUCTION AND PURPOSE D1-1
1.2 GENERAL PRINCIPLES OF EXPOSURE ASSESSMENT D1-2
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PART D - CHAPTER 1
FUNDAMENTALS OF EXPOSURE AND RISK ASSESSMENT

1.1 INTRODUCTION AND PURPOSE

Series 875, Group B provides guidance for conducting postapplication exposure monitoring studies. The results of these studies are used to characterize risks to humans from reentering areas that have been treated with chemical substances such as pesticide products. This information may be used to evaluate risks associated with specific chemical uses, to determine appropriate regulatory options such as setting restricted-entry intervals for agricultural applications, or to determine whether products can be used in and around the home without appreciable risks to humans.

The risk assessment process estimates the likelihood and magnitude of human health effects that result from environmental exposure. Four steps make up EPA's risk assessment process: hazard identification, dose/response assessment, exposure assessment, and risk characterization. These are briefly defined below:

- Hazard Identification. EPA evaluates a pesticide's inherent toxicity (i.e., the types and degrees of harmful effects a pesticide may cause). This is done principally by evaluating laboratory studies conducted on animals. For example, laboratory studies attempt to determine if a chemical is an eye irritant, causes acute poisoning, causes birth defects, or causes cancer, among other effects.

- Dose-Response Assessment. A pesticide's potential for causing adverse health effects is identified through a battery of short-term or acute, intermediate or subchronic, and long-term or "chronic" toxicity testing. In several series of tests, laboratory animals are exposed to different doses of a pesticide, and EPA scientists evaluate the test results to determine the level of exposure in each of those studies that did not cause any noncancer effect. Dose-response assessment is the process of characterizing the relationship between the magnitude of exposure (i.e., doses) and the occurrence of health effects in the foregoing studies.

- Exposure Assessment. Once harmful health effects are identified in the laboratory tests, EPA must estimate the level, duration, frequency, and route of exposure for people.

- Risk Characterization. Risk characterization involves describing the nature and magnitude of the risks by integrating the above factors. By combining estimates of likely or actual pesticide exposure with the toxicity of the pesticide, EPA can characterize the risks that it poses. Simply stated,

$$RISK = Toxicity \times Dose \qquad \text{(Eq. D1-1)}$$

The purpose of Part D, Chapter 1 of these Guidelines is to provide users with basic guidance on the principles of exposure and risk assessment. Part D, Chapter 2 provides users with specific guidance for conducting exposure and risk assessments for postapplication pesticide exposure scenarios. Because the process of identifying hazards, establishing dose response relationships, and determining dietary exposure is beyond the scope of Series 875, Group B, only exposure and risk assessment calculations are included in Part D.

1.2 GENERAL PRINCIPLES OF EXPOSURE ASSESSMENT

Exposure assessment is the process by which: (1) potentially exposed populations are identified; (2) potential pathways of exposure are identified; and (3) chemical intakes/potential doses are quantified. Exposures to pesticides may occur by oral, inhalation, or dermal absorption routes. ***Exposure*** is commonly defined as contact of visible external physical boundaries (i.e., external boundaries such as the mouth, nostrils, and skin) with a chemical agent (U.S. EPA, 1992). As described in the *Guidelines for Exposure Assessment*, exposure is dependent upon the intensity, frequency, and duration of contact. The intensity of contact is typically expressed in terms of the concentration of contaminant per unit mass or volume (i.e., μg/g, μg/L, mg/m^3, ppm, etc.) in the media to which humans are exposed (U.S. EPA, 1992).

Dose refers to the amount of chemical to which individuals are exposed that crosses the external boundary (U.S. EPA, 1992). Dose is dependent upon contaminant concentration and the rate of intake (i.e., inhalation or ingestion) or uptake (i.e., dermal absorption) and may be normalized to body weight as a function of time (i.e., mg/kg/day). ***Potential dose*** is the amount of chemical which could be ingested without cooking or cleaning the food or filtering the water, which could be inhaled without wearing a respirator, or which would be deposited upon the skin without clothing. ***Applied dose*** is the amount of chemical that is actually ingested into the gastrointestinal tract (after food preparation or water treatment), inhaled into the lung (after accounting for the effects of a respirator or particle deposition in the upper airways), or reaches the skin (after penetration through gloves and clothing). Applied dose has sometimes been called ***delivered or deposited dose***. The ***internal dose*** is the amount of chemical absorbed into the body through the gastrointestinal tract, lung or skin. Internal dose has sometimes been called ***absorbed dose***. The toxicologic basis for risk assessment is typically either the applied dose from animal feeding studies or the internal dose from pharmacokinetic studies followed by intraperitoneal or other injected delivery into the test animal. Field studies using either passive dosimetry (see Part B, Chapter 7) or air monitoring (see Part B, Chapter 8) yield either potential or applied doses which can be related to internal dose through absorption factors. Biological monitoring (see Part B, Chapter 10) yields data which can be related to either applied dose or internal dose through pharmacokinetic models. These latter relationships are discussed in Part D, Chapter 2. Potential dose may be calculated as follows:

$$DR_{pot} = C \times CR \tag{Eq. D1-2}$$

where:

DR_{pot} = potential dose rate (mg/day);

C = contaminant concentration in the media of interest (mg/cm^2; mg/m^3, mg/g); and

CR = contact rate with that media (cm^2/day; m^3/day; g/day).

The contaminant concentration is the amount of pesticide in the media to which humans are exposed. The contaminant concentration may be affected by dissipation of chemical over time by evaporation, degradation or other fate processes. Contact rate may be defined as the rate of ingestion, inhalation, or dermal absorption or as the transfer coefficient (U.S. EPA, 1989a).

Potential doses may also be averaged over body weight and time (mg/kg/day) to calculate an average daily dose. Average daily potential dose rates may be estimated using the standard exposure assessment algorithm shown below (U.S. EPA, 1992).

$$ADD_{pot} = [C \times CR \times ED \times F] \; / \; [BW \times AT] \tag{Eq. D1-3}$$

where:

ADD_{pot} = potential average daily dose (mg/kg/day);

C = contaminant concentration (mg/L, mg/m^3; mg/cm^2);

CR = contact rate (L/day; m^3/day; cm^2/day);

ED = exposure duration (years);

F = frequency of exposure events (days/year);

BW = body weight (kg); and

AT = averaging time (days).

Equation D1-3 is structured to facilitate averaging intermittent or seasonal exposure patterns over one or more years. As described above, the contaminant concentration refers to the amount of chemical residue in the media of interest, and contact rate refers to the rate of ingestion, inhalation, or dermal deposition per day. Exposure duration refers to the length of time that contact occurs and is affected by activity patterns; for instance, one year to calculate annual average. Frequency is the number of exposure events over a specified time period. Body weight and averaging time are specific to the population and exposure scenarios being evaluated. The averaging time (AT) is the number of days over which the exposure is averaged. For exposure assessments used to support cancer risk assessments AT is replaced by lifetime (LT) (i.e., 25,550 days = 70 years * 365 days/year). The resulting exposure estimate is referred to as the potential lifetime average daily dose ($LADD_{pot}$). ADD_{pot} and $LADD_{pot}$ are expressed in units of mg/kg/day. Absorbed doses (i.e., ADD_{abs} and $LADD_{abs}$) may be estimated by applying an absorption factor.

Average, high-end, and/or bounding estimates may be made using these algorithms. These exposure descriptors account for individual and population variability and represent points on the distribution of exposures. Average dose rates represent the mean and may be estimated using central tendency values for all the parameters in the ADD or LADD. The high-end potential dose rate (90th or 95th percentile) is a reasonable approximation of dose for individuals at the upper end of the distribution of exposures (U.S. EPA, 1992). High-end values are estimated by setting some, but not all, ADD or LADD parameters to the upper-end values. Finally, bounding potential dose rates are exposures that are estimated to be greater than the highest individual exposure in the population of interest. Bounding estimates are often used in screening-level assessments.

1.3 GENERAL PRINCIPLES OF RISK ASSESSMENT

Risk characterization integrates toxicity and exposure data to provide quantitative estimates of carcinogenic risk and systemic hazards. Carcinogenic risks represent the incremental probability that an individual will develop cancer over a lifetime as a result of exposure to a chemical compound. EPA usually assumes a non-threshold dose-response for carcinogens (i.e., some finite risk no matter how small the dose). For pesticides with carcinogenic endpoints, individual lifetime risk is estimated by multiplying the $LADD_{pot}$ by the cancer potency slope factor as follows:

$$R_i = LADD_{pot} \ x \ SF \qquad \text{(Eq. D1-4)}$$

where:

R_i = excess individual lifetime cancer risk level (unitless);

$LADD_{pot}$ = lifetime average potential daily dose (mg/kg/day); and

SF = cancer potency slope factor $(mg/kg/day)^{-1}$ (also known as Q_1^*).

R_i represents the probability of excess cancer cases over a lifetime. For example, a risk level of 10^{-6} indicates that an excess cancer case is projected to occur in no more than 1 out of a million individuals exposed to this LADD over a lifetime. Annual excess cancer risks may be estimated by dividing the lifetime risk value by the average lifetime (70 years). LADDs are calculated as described previously. Slope factors are conservative estimates of the incremental probability of cancer from a unit dose of chemical over a lifetime. They are chemical-specific values derived from animal toxicity studies and or human epidemiological data and represent the upper 95 percent confidence interval.

Population risks represent conservative estimates of the number of individuals in an exposed population that are likely to be affected by pesticide exposure. Population risks are calculated as follows.

$$POP_{risk} = R_i \times POP_{exposed} \qquad \text{(Eq. D1-5)}$$

where:

POP_{risk} = population risks (number of individuals in an exposed population that are projected to be affected);

R_i = excess individual lifetime cancer risk level (unitless); and

$POP_{exposed}$ = population exposed (number of exposed individuals in the population).

For chemicals with noncancer endpoints (i.e., systemic effects) where a threshold dose-response relationship is assumed, hazard quotients are calculated to characterize the risks associated with exposure. Hazard quotients are unitless values that are calculated by dividing the average daily dose by a value that represents a toxicity endpoint and are calculated as follows.

$$H = ADD \,/\, RfD \qquad \text{(Eq. D1-6)}$$

where:

H = hazard quotient (unitless);

ADD = average daily dose (mg/kg/day); and

RfD = reference dose or other datum indicative of the toxicity endpoint of interest (mg/kg/day).

If the hazard quotient is greater than one, an effect would be expected; but if the ratio is less than one, no effects would be expected. Typically, the reference doses used in these calculations are values below which no adverse health risks would be expected. They are derived by dividing NOAELs by uncertainty and safety factors. RfDs have been developed by EPA for numerous chemical substances based on available animal toxicity data and human epidemiological data.

Noncarcinogenic risks can also be represented as the margin of exposure (MOE). The MOE represents the ratio of a NOAEL to an estimated dose/exposure level. MOEs are calculated as follows:

$$MOE = NOAEL/ADD \qquad \text{(Eq. D1-7)}$$

where:

MOE = margin of exposure (unitless);

NOAEL = no observable adverse effect level (mg/kg/day); and

ADD = average daily dose (or absorbed dose) (mg/kg/day).

High MOE values (i.e., values greater than 100) may imply a low level of concern. In contrast, low MOE values may imply high levels of concern. Further interpretation of the MOE value is dependent on whether the toxicity data are from animals or humans. It should be noted that neither hazard quotients nor MOEs are probabilistic statements of risk. It should also be noted that the use of either potential or absorbed doses is dependent on the nature of the toxicity endpoint. For example, if the toxicity data (e.g, NOEL) are based on an applied dose, ADD_{pot} or $LADD_{pot}$ values should be used. However, if the toxicity data are based on an internal dose, ADD_{abs} or $LADD_{abs}$ values should be used.

1.4 INPUTS AND STANDARD ASSUMPTIONS USED IN EXPOSURE/RISK ASSESSMENT

Inputs for the standard exposure/risk calculations described above should be representative of the population/scenarios being evaluated. Contaminant concentration values are generated based on residue and dissipation data collected at the site for the media of interest. Factors such as frequency and duration of use can be derived from actual data on the activities/uses associated with site/scenario-specific uses of a chemical, or from general population survey data on activity patterns and product usage. Other inputs to the exposure calculations such as contact rate (ingestion rate, inhalation rate, skin surface area), body weight, and lifetime may be based on standard exposure factors. Mean and upper-percentile exposure factors based on distributions of data collected from the scientific literature are reported in EPA's *Exposure Factors Handbook* (1989a) and EPA's *Risk Assessment Guidance for Superfund* (1989b). Recommended standard exposure factors for use in postapplication exposure assessments are summarized in Part D, Chapter 2. Slope factors and reference doses used in calculating risks and hazards can be obtained from EPA's *Integrated Risk Information System (IRIS)*, EPA's *Health Effects Assessment Summary Tables (HEAST)*, or by contacting EPA's Human Health Assessment Group.

1.5 CHARACTERIZING EXPOSURE/RISK

Risk characterization provides decision makers with a qualitative evaluation of the accuracy of the risk estimates. In characterizing risks from exposure to chemical substances, the variability and uncertainty associated with the exposure/risk estimates should be addressed. The risk characterization should provide information on: (1) potential measurement errors based on the precision and accuracy of the available data, (2) variability of the input data used in the exposure/risk estimates, and (3) uncertainty that results from data gaps or the assumptions used. The risk characterization also assesses the relative importance of these components on the estimates of exposure/dose and risk.

Uncertainty may be introduced into the exposure/risk calculations at various stages of the risk assessment process. Uncertainty may occur as a result of: (1) the techniques used to sample and analyze chemical residues, (2) chemical fate and transport factors, (3) the selection of exposure scenarios and exposure factors, (4) the uncertainties associated with toxicity data that have been extrapolated from high doses in animals to low doses in humans, and that do not account for the interactions of exposures to multiple chemical substances over a lifetime, and (5) the potential size of the exposed populations and subpopulations. Variability can occur as a result of variations in individual day-to-day or event-to-event exposure factors or variations among the exposed population. Variability can be addressed by estimating exposure for the various descriptors of exposure [i.e., central tendency (mean or median), high-end (90th or 95th percentile), or bounding (100th percentile)] to represent points on the distribution of exposures.

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PART D - CHAPTER 2
CALCULATIONS

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PART D - CHAPTER 2
CALCULATIONS
GUIDELINE 875.2900

2.1 INTRODUCTION AND PURPOSE

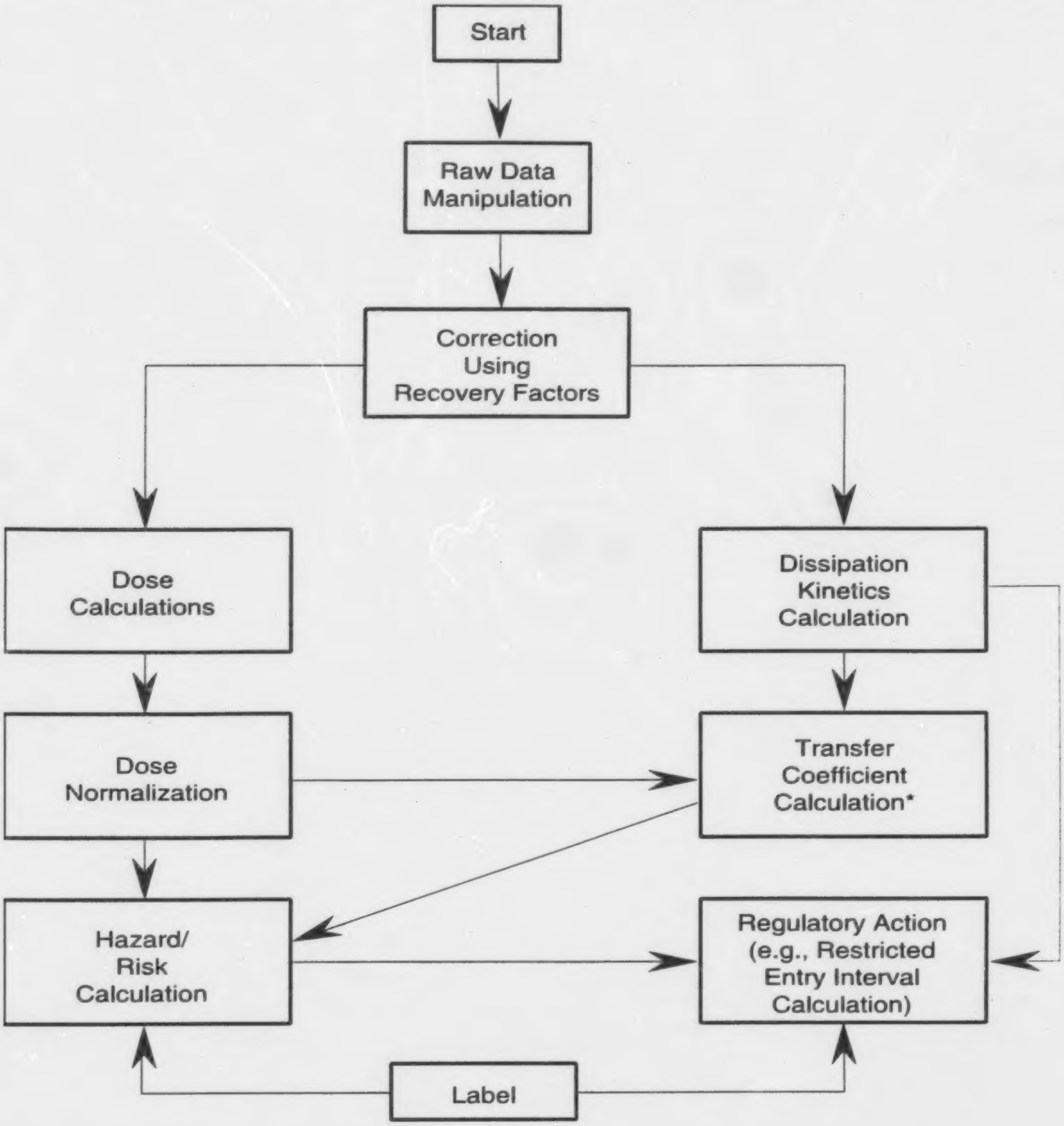
The purpose of this chapter is to provide users of Series 875, Group B with guidance for completing exposure and hazard or risk assessments. Quantitative approaches for analyzing nondietary hazards or risks to humans resulting from entry into areas previously treated with a chemical are addressed in this chapter. Both residential and occupational uses of chemicals, as well as any other chemical use scenario of concern regulated by FIFRA, are included. These include uses of, or exposures to, either pesticides or antimicrobials by agricultural workers, industrial workers, homeowners and occupants (lawncare, garden, and indoors), swimmers, and children through nondietary ingestion. The calculations presented in this chapter are based on the generally accepted fundamentals of exposure and risk assessment described in Part D, Chapter 1 that are summarized from U.S. EPA Guidelines for Exposure Assessment (U.S. EPA, 1992). In order to better understand the concepts and principles described in this chapter, a flow chart has been developed that details each major calculation, the logical progression of an analysis, the required analysis inputs, and standard outputs expected (See Figure D2-1.) The specific areas for which calculations are addressed in this chapter include: commonly used formulas; chemical data; exposure/dose calculations; chemical dissipation kinetics; transfer coefficients; risks, hazards, and Restricted-Entry Intervals. The nomenclature used to describe all calculations in this chapter is based on the guidance provided in the U.S. EPA's Exposure Assessment Guidelines (U.S. EPA, 1992).

2.2 COMMONLY USED FORMULAS AND APPROACHES

This section describes statistical formulas and approaches that are common to the calculations described in this chapter. These items are described in this section because they have utility in several calculations and are referenced in this chapter frequently.

2.2.1 Statistical Formulas

The most common statistical calculations required to manipulate the types of data described in this Guideline include the following: arithmetic mean, geometric mean, standard deviation (σ), coefficient of variation, 95 percent confidence interval, and linear regression. The arithmetic mean is a simple average. Geometric mean values are calculated by computing the arithmetic mean of log


Start
Raw Data Manipulation
Correction Using Recovery Factors
Dose Calculations
Dissipation Kinetics Calculation
Dose Normalization
Transfer Coefficient Calculation*
Hazard/ Risk Calculation
Regulatory Action (e.g., Restricted Entry Interval Calculation)
Label

*Calculation scheme is simplified if adequate transfer coefficients are available (i.e., dose calculations are simplified)

Figure D2-1. Calculation Progression Flowchart

transformed data and then calculating the anti-log of the computed mean. Standard deviation is a measure of the variance of the data and can be computed using standard statistical methods. Calculation of the coefficient of variation and the 95 percent confidence interval can be completed as follows:

$$CV = [100 * (SD / \bar{x})] \qquad \text{(Eq. D2-1)}$$

Where:

CV = coefficient of variation (percent);
SD = standard deviation; and
$\bar{x}$ = mean.

$$95\%\ CI = [\bar{x} \pm ((SD * 1.96)/\sqrt{N})] \qquad \text{(Eq. D2-2)}$$

Where:

95% CI = 95% confidence interval;
$\bar{x}$ = mean;
SD = standard deviation; and
N = number of datapoints included in calculation.

Linear regressions can be completed using commonly available software packages. Investigators should specify the software and version used for all calculations.

2.2.2 Appropriate Use of Quantification/Detection Limits

Proper definition of the limit of detection (LOD) and limit of quantification (LOQ) for every sample matrix and dosimeter used in a study is critical in all calculations. (See Part B, Chapter 1 and Part C for a detailed explanation.) Historically, the Agency has used one-half of the LOQ to represent chemical concentrations in a matrix when the residue level in that matrix is at or below the assigned LOQ. Using the definitions of LOD and LOQ in Section 1.2 (or quantitatively similar), allows somewhat more qualitative latitude for sample results that are also below the assigned LOD. The following matrix can be used to decide what value should be selected for use in any calculation.

If $X > LOQ$, Use X

If $LOD < X \leq LOQ$, Use 1/2 LOQ

If $X \leq LOD$, Use 1/2 LOD

Where:

X = measured chemical concentration

Investigators should indicate whether calculated values are based on values that are either one-half the LOQ or one-half the LOD. This is necessary for the Agency to adequately interpret study results.

2.3 CHEMICAL DATA

Calculations required to manipulate raw residue chemistry data and the techniques required to correct raw data for the appropriate quality control results are addressed in this section.

2.3.1 Basic Manipulation of Raw Data

Postapplication exposure and chemical dissipation data are typically generated from one or more of the following types of samples: (1) quality control for all matrices; (2) environmental matrices (e.g., soils); (3) transferable/dislodgeable matrices (e.g., foliar dislodging solutions); (4) filters used for air monitoring; (5) passive dosimeters (e.g., patches, whole-body dosimeters, cotton sample gloves); and (6) biological matrices (e.g., urine or blood). For the purposes of this section, environmental and transferable data will be treated similarly as will any filter and passive dosimeter data.

Quality Control Data may include, but are not limited to, the following: formulation characterization, tank mix solution analysis, field recovery, laboratory recovery, storage stability, and travel spikes. (See Part C - Quality Assurance/Quality Control for further information.) Data from blank samples should be manipulated on a case-by-case basis (e.g., a mean and standard deviation might be calculated for blank samples that contain residue levels). The following information and summary statistics must be provided and/or calculated for all other samples:

- Means and standard deviations of the recovery values over each and over all fortification levels on each matrix;
- Coefficients of variation of the recovery values over each and over all fortification levels on each matrix; and
- 95 percent confidence interval of the mean recovery values (upper and lower limits) over each and over all fortification levels on each matrix.

Environmental Matrix Data are based on environmental and transferable/dislodgeable sampling methods. These data may include, but are not limited to, the following: dislodgeable foliar residue data, soil residue data, carpet residue data, ambient air monitoring data, and wipe tests. Unit residue levels should be calculated (e.g., $\mu g/cm^2$ values for DFR based on the double-sided leaf area of the sample). After this normalization, minimal manipulation of the data is required until corrected for the appropriate quality control results. These data correction procedures are described below.

In cases where a typical Iwata leaf punch is used, the sample surface area is simply calculated by multiplying the number of leaf punches by the surface area of each leaf disc in a sample (double-sided). In cases where the use of a leaf punch is not feasible, the weights of individual samples are recorded and then multiplied by a unit leaf area factor to determine the total area of individual samples. Unit leaf area factors establish a relationship between the weight of a leaf type and the surface area of the leaf type. Investigators may use either a simple proportion or a linear regression to represent the relationship between leaf surface area and sample weight. Using the simple proportion method, sample leaf surface area can be calculated as follows:

$$LA_{sample} = ULAF \times SW_{DFR} \qquad \text{(Eq. D2-3)}$$

Where:

LA_{sample} = leaf area of DFR sample used for all calculations (cm^2);

$ULAF$ = unit leaf area factor used for all calculations (cm^2/gram); and

SW_{DFR} = weight of sample collected and analyzed in the determination of dislodgeable foliar residues (grams).

$$ULAF = LA_{ulaf}/SW_{ulaf} \qquad \text{(Eq. D2-4)}$$

Where:

$ULAF$ = unit leaf area factor which can be used to calculate the sample surface area from sample weight (cm^2/gram);

LA_{ulaf} = surface area of leaf sample collected and analyzed in the determination of the ULAF (cm^2); and

SW_{ulaf} = weight of sample collected and analyzed in the determination of the ULAF (grams).

The equation for the linear relationship option is shown below:

$$LA_{sample} = (S * SW) + b \qquad \text{(Eq. D2-5)}$$

Where:

LA_{sample} = leaf area of DFR sample used for all calculations (cm^2);

S = slope of line generated during previous linear regression of data (cm^2/gram of sample weight of leaves designated for surface area determinations);

SW = weight of DFR sample (grams); and

b = y intercept of the linear equation generated during previous regression (cm^2).

Passive Dosimetry human exposure monitoring data may include, but are not limited to, the following: patches; whole-body dosimeters; inhalation filters, resins, polyurethane foam, or impinger solutions; cotton gloves; and aqueous handwash solutions.

If the Durham and Wolfe patch technique is used, dermal exposure levels should be calculated based on the surface area of each set of dosimeters in units of $\mu g/cm^2$. These values should represent the collection patterns described in Part B. If whole-body dosimetry is used, the raw data should be reported in units of μg/sample for each body part sampled. The conversion of patch data to units of μg/sample, for comparison to whole body dosimeters data, are only generated after corrections for recovery efficiency have been made and the data are adjusted for body surface areas.

As with whole body dosimetry data, no manipulation of hand exposure data is required to yield data in units of μg/sample. Hand exposure data can represent both hands combined, or individual hands. Investigators must consider their quality control regimen when designing a sequential sample study. For example, if over the course of an 8-hour monitoring interval more than one set of field recovery samples were generated (e.g., AM and PM), then the raw data should be grouped to enable the appropriate application of recovery correction factors to the raw data within each group.

Generally, raw inhalation exposure data should be divided by the air volume represented by the air sample to yield values in units of $\mu g/m^3$. Any sequential air concentration data should be grouped in a manner similar to that described above for dermal hand data. Sequential air sampling is common for some analytes on some sample media (e.g., where exceeding the sample loading capacity would result in breakthrough, or retention characteristics may limit the sample duration).

Biological Monitoring data may include, but are not limited to, the following: chemicals excreted in the urine or blood. Results based on these data should be calculated as individual replicate sample results, in the appropriate units, collected at specific sampling intervals and for specific test subjects (e.g., total excreted in urine over a 24-hour interval for each individual test subject). The format for calculating results based on biological monitoring data is dependent upon the pharmacokinetics of the pesticide of interest and must be reflective of the biological processes monitored to determine exposure (e.g., the urine excretion profile).

2.3.2 Corrections Based on Quality Control Data

Correcting residue levels based on the quality control data generated in a study is required to accurately account for residue losses and chemical transformations that may occur during the conduct of a study (i.e., after collection of a residue by a dosimeter/sample matrix and prior to quantitation during analysis). Raw residue data must be corrected for recovery if any appropriate recovery correction factor is less than 90 percent. Recovery correction factors and the equations used to calculate them for each sample matrix are described below:

$$RCF = ((FR/100) * (LR/100) * (SS/100)) \qquad \text{(Eq. D2-6)}$$

Where:

RCF = recovery correction factor which is applied to raw residue data as shown in Eq. D2-7 (unitless);

FR = arithmetic mean field recovery for matrix (%);

LR = arithmetic mean lab recovery for matrix (%); and

SS = arithmetic mean storage stability recovery for matrix (%).

As described in Part C, various combinations of recovery data may be generated in a study. Therefore, it is the investigators responsibility to determine which quality control data are the appropriate basis for a correction factor. For example, if a field recovery sample is generated concurrently with an actual exposure sample, then stored and analyzed concurrently with the field exposure samples, only a correction for that field recovery sample analytical result is required. Investigators must make judgements concerning this issue and clearly explain/illustrate how residue data were corrected for recovery in any submission to the Agency. It is not routine to correct residue data based on the results of formulation characterization data or the results of a tank mix analysis. If raw data are corrected, a thorough explanation of the data that initiated such a correction is required (e.g., provide fate data to document hydrolytic instability in a DFR wash solution).

After all correction factors have been calculated, raw residue data must be corrected using the appropriate factors. Investigators must clearly indicate in any submission to the Agency which RCF values are to be used to correct specific sets of raw residue data. The equation that describes this correction process is presented below:

$$C_{cor} = (C_{raw})/(RCF) \qquad \text{(Eq. D2-7)}$$

Where:

C_{cor} = corrected chemical value which serves as the basis for all exposure and chemical dissipation calculations (e.g., μg/sample or $\mu g/cm^2$);

C_{raw} = raw chemical value which represents data obtained directly from instrument prior to any process that corrects the result based on the quality control regimen of the study (e.g., μg/sample or $\mu g/cm^2$); and

RCF = recovery correction factor. (See Eq. D2-6 above.)

2.4 EXPOSURE/DOSE CALCULATIONS

Algorithms necessary to quantify dose levels for postapplication chemical exposure scenarios are presented in this section. A complete hazard or risk analysis requires the calculation of exposure/dose levels for each route of exposure that is of concern for the specific chemical use scenario (e.g., dermal, inhalation, and/or nondietary ingestion) or a thorough analysis of available biological monitoring data. The basic elements that are required in such calculations are described in this section. These elements include the calculation of exposure, potential dose, or internal dose levels; normalization of exposure/dose levels; and completion of all required statistical manipulations of the normalized values. Please refer to Part D, Chapter 1, Figure D2-2, and the U.S. EPA Guidelines for Exposure Assessment for clarification regarding the nomenclature used in these calculations (U.S. EPA, 1992).

2.4.1 Calculation of Exposure and Potential Dose

For the dermal route, potential dose represents the amount of chemical residues that are deposited onto the skin (U.S. EPA, 1992). For the oral and inhalation routes, potential dose represents the concentration available for intake through the mouth or nose while potential dose represents the amount inhaled or taken in through the mouth and nose (U.S. EPA, 1992). The potential dose calculations described in this section may be used to summarize all types of human exposure monitoring data, regardless of the techniques used to generate the data (i.e., passive dosimetry or biological monitoring). Potential dose levels are a required aspect of all calculations based on passive dosimetry. However, for biological monitoring techniques, the calculation of potential dose levels is only an exercise that enables activity/job specific transfer coefficients to be calculated by back calculating to potential dose levels. (See Figure D2-1 above and Section 2.6 below.)

Dermal Passive Dosimetry techniques can be categorized based on the nature of the monitoring devices/matrices (e.g., dermal-nonhand and dermal-hand). Algorithms required for calculations specific to each dosimeter type are presented below. Dermal potential dose levels based on patch dosimetry data for nonhand body parts must be calculated using the equation below with standard surface areas for each body part:

$$D_{\text{pot. dermal (body part)}} = C_{\text{cor-patch}} * SA \qquad \text{(Eq. D2-8)}$$

Where:

$D_{\text{pot. dermal (body part))}}$ = exposure for specific nonhand body parts (μg/body part);

$C_{\text{cor-patch}}$ = corrected patch concentration as described in Eq. D2-7 ($\mu g/cm^2$); and

SA = human skin surface areas for body parts of interest (cm^2/body part).

[Please refer to EPA's Exposure Factors Handbook for appropriate human skin surface areas (U.S. EPA, 1996).] The total, nonhand, potential dermal dose ($D_{\text{pot. dermal (nonhand)}}$) is the sum of all $D_{\text{pot. dermal (body part)}}$ across all body parts.

Whole-body dosimeters and glove dosimeters cover each body part of interest during sampling by design (e.g., long-sleeved shirt over the torso and arms). As a result, no further calculation is

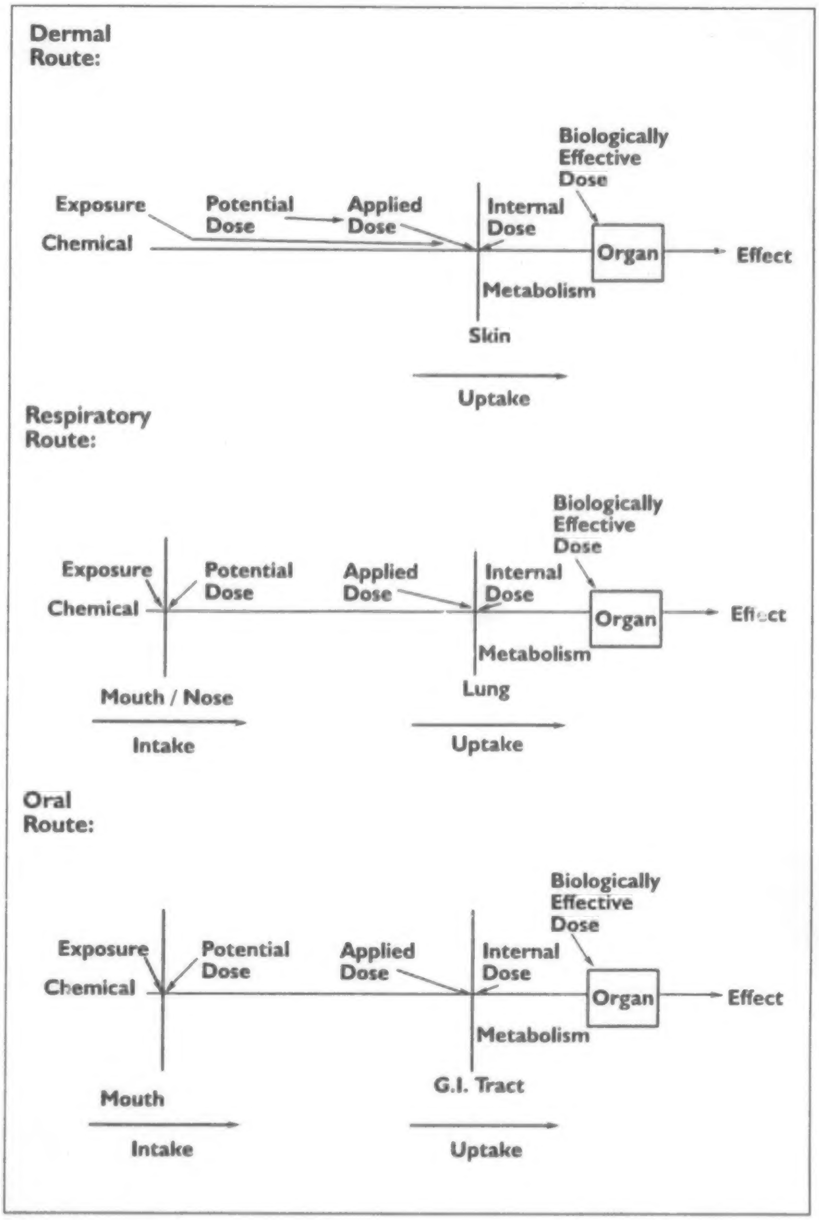

Dermal Route:
Biologically Effective Dose
Exposure
Potential Dose
Applied Dose
Internal Dose
Chemical
Organ
Effect
Metabolism
Skin
Uptake
Respiratory Route:
Biologically Effective Dose
Exposure
Potential Dose
Applied Dose
Internal Dose
Chemical
Organ
Effect
Metabolism
Mouth / Nose
Lung
Intake
Uptake
Oral Route:
Biologically Effective Dose
Exposure
Potential Dose
Applied Dose
Internal Dose
Chemical
Organ
Effect
Metabolism
Mouth
G.I. Tract
Intake
Uptake

Figure D2-2. Schematic of Dose and Exposure

Source: U.S. EPA, 1992

required other than a summary calculation if the dosimeter garments are sectioned prior to analysis. Dermal hand measures are similar to the whole-body dosimeter data in that they require either no or few calculations. If only one hand monitoring sample was collected, its corrected result is the measured potential dose. If multiple samples were collected during a monitoring period, a cumulative potential dose value must be calculated by adding the values from all intervals. (See Section 2.3.1 for further information.)

The total potential dermal dose for each test replicate can be calculated using the results of the calculations described above and the following equation:

$$D_{\text{dermal (tot. pot.)}} = D_{\text{pot. dermal (hand)}} + D_{\text{pot. dermal (nonhand)}} \qquad \text{(Eq. D2-9)}$$

Where:

$D_{\text{dermal (tot. pot.)}}$ = cumulative potential dermal dose during a replicate, term may represent several dosimeter samples collected from a single exposure replicate (μg or mg/replicate);

$D_{\text{pot. dermal (hand)}}$ = cumulative potential dermal dose to the hands during a replicate (μg or mg/replicate); and

$D_{\text{pot. dermal (nonhand)}}$ = potential dermal dose for nonhand body parts of interest (μg or mg/replicate).

Inhalation Dosimetry techniques can be categorized based on the nature of the monitoring devices/matrices (e.g., personal sampling pump or passive badge-type monitor). The algorithm required for calculations specific to the use of filters and sampling pumps (i.e., the most common monitoring approach) is presented below. Investigators should refer to the calculations presented in the User's Manuals for passive, badge-type monitors as these types of calculations are usually specific to the device. Potential inhalation dose for personal monitoring completed using a filter and pump device, excluding passive badge-type monitors, is most often calculated using the equation below:

$$D_{\text{inh(tot. pot.)}} = (C_{\text{cor-inhalation}} * \text{IR/FR}) \qquad \text{(Eq. D2-10)}$$

Where:

$D_{\text{inh(tot. pot.)}}$ = cumulative potential inhalation dose during a replicate; term may include several iterations of this equation that represents several samples collected from a single exposure replicate (μg or mg/replicate);

$C_{cor\text{-}inhalation}$ = corrected chemical levels measured on inhalation monitor as described in Eq. D2-7 above (μg or mg/sample);

FR = sampling pump flow rate (L/min); and

IR = inhalation rate for people as they perform various types of tasks/activities as presented (L/minute).

[Please refer to EPA's Exposure Factors Handbook for appropriate human inhalation rates (U.S. EPA, 1996).]

Equation D2-10 presented above is a calculation that summarizes the following equations commonly used in industrial hygiene for presenting air monitoring data and calculating inhalation dose. These equations include calculating sample volumes, chemical concentrations, and inhalation dose using a human inhalation rate. Air sample volume can be calculated using the following equation:

$$V = FR \times ED \qquad \text{(Eq. D2-11)}$$

where:

V = air volume for sample (L);
FR = sampling pump flow rate (L/min); and
ED = exposure duration or length of sample collection interval (min).

The next step in the process is to calculate the exposure concentration (i.e., monitored airborne concentration). In some cases, these exposure concentration values are compared directly with a toxicology endpoint presented as a concentration (e.g., dose concentrations for a 90-day subchronic inhalation study). Exposure concentrations can be calculated using the following equation:

$$C_{air} = C_{cor\text{-}inhalation} / V \qquad \text{(Eq. D2-12)}$$

where:

C_{air} = corrected chemical airborne exposure concentration measured during a single exposure replicate (μg/L);

$C_{cor\text{-}inhalation}$ = corrected chemical levels measured on inhalation monitor as described in Eq. D2-7 above (μg); and

V = air volume for sample (L).

Inhalation dose can then be calculated using the exposure concentration and a human inhalation rate. This calculation of inhalation dose can be used to substitute for the inhalation dose calculation illustrated in Eq. D2-10. Inhalation dose, using Eq. D2-11 and D2-12, can be calculated using the following equation:

$$D_{inh\,(tot.\,pot.)} = C_{air} * IR * ED * CF \qquad \text{(Eq. D2-13)}$$

where:

$D_{inh\,(tot.\,pot.)}$ = cumulative potential inhalation dose during a replicate; term may represent several samples collected from a single replicate (mg/replicate);

C_{air} = corrected chemical airborne exposure concentration measured during a single exposure replicate (μg/L);

IR = inhalation rate for people as they perform various types of tasks/ activities (L/minute);

ED = exposure duration or length of sample collection interval (min.); and

CF = weight conversion factor (1 mg/1,000 μg).

It should be noted that Equations D2-10 through D2-13 apply to monitoring based on the use of sampling pumps and filters. With appropriate modification, the same basic equation can be used for various other types of less common monitoring protocols (e.g., stationary high-volume samples may require altering the units). Investigators must document any modifications of the equation that are used in calculations.

Biological Monitoring data may be used to estimate activity-specific transfer factors. A key step in this process is to back calculate potential dose levels. The pharmacokinetic model for each specific analyte of concern must be used to calculate potential dose levels. Investigators must clearly demonstrate the calculations used to define potential dose levels based on biological monitoring data as well as any assumptions pertaining to the relative impact of each exposure route.

2.4.2 Calculation of Internal Dose Levels

Internal dose levels can be calculated using either passive dosimetry data in conjunction with the appropriate absorption factors or using biological monitoring data in conjunction with a pharmacokinetic model. The requirements for calculating internal dose levels depend upon the nature of the toxicological data base. For example, if the toxicological endpoint of concern is based on a dermal application study (e.g., 21 day dermal subchronic), then an internal dose calculation is not required because potential dose levels can be directly compared to the endpoint in any hazard or risk analysis. However, if the toxicological endpoint of concern is based on an oral study, then an internal dose may well be the common denominator by which the oral no effect level from ingestion can be compared to a potential dermal or inhalation dose. For the purpose of this guideline, oral and inhalation potential dose levels will be considered similar to oral and inhalation internal dose levels because data are generally not available to assess the biological pathways that determine internal dose from a potential dose value (i.e., AF in Eq. D2-14 is 100 percent unless chemical/scenario specific data are available). In order to make that comparison, one must be able to calculate an internal dose from the route of exposure that created the toxicologic endpoint of concern.

Passive Dosimetry data are used initially to calculate potential dermal and inhalation dose levels as described in Section 2.4.1 above. Using these values, the following equation can be used to calculate internal dose levels:

$$D_{int} = ((D_{dermal\ (tot.\ pot.)} * AF) / 100) + ((D_{inh\ (tot.\ pot.)} * AF)/100) \qquad \text{(Eq. D2-14)}$$

Where:

D_{int} = internal dose based on route of exposure (μg or mg/replicate) (see Eq. D2-9);

$D_{dermal\ (tot.\ pot.)}$ = potential dermal dose (μg or mg/replicate) (see Eq. D2-9);

$D_{inh\ (tot.\ pot.)}$ = potential inhalation dose (μg or mg/replicate) (see Eq. D2-10); and

AF = absorption factor through a biological membrane or barrier (%) (e.g., percutaneous absorption).

Biological Monitoring data are typically presented as an internal dose level. Based on the pharmacokinetics of the analyte of interest, investigators must demonstrate a clear calculation of internal dose. Further description of such calculations within these guidelines would not be appropriate as several types of chemical specific, biological processes can be monitored to quantify exposure levels to a chemical.

2.4.3 Unit Dose Levels

The calculation of unit levels is a process by which the total dose levels are normalized based on parameters such as duration of each replicate or the productivity of work during the exposure replicate (e.g., pounds harvested, acres mowed, etc.). These normalization factors are typically parameters that are expected to fluctuate with the accompanying dose levels. Dose data presented on a unit basis are easily compared with similar data from other types of activities/job functions to establish a ranking between various scenarios to determine which activities are of highest concern. Unit dose levels can be calculated with data that indicate the duration of the exposure replicate or the activities of the test subject during each replicate (e.g., time during an activity such as harvesting or pounds of crop picked such as tomatoes or grapes). Potential or internal dose levels are used in the calculation depending upon the toxicological properties of the chemical, as defined by available data, the design of the study, and the objective of the assessment. The following algorithm is suggested for the normalization of data:

$$D_{unit} = D_{rep}/NF$$

Where:

D_{unit} = unit dose level which has been normalized by time, activity, or some other factor; doses are normally reported as μg/hour or μg/activity;

D_{rep} = total dose incurred by each test subject during an exposure replicate; and

NF = factor selected by investigators upon which to normalize dose levels for each test subject in a study (e.g., duration of exposure monitoring period, level of activity throughout the exposure replicate, or some other parameter identified by the investigator).

Investigators may opt to normalize data based on some type of data other than the two options provided above. If this is the case, investigators must provide a detailed justification for the selection.

2.4.4 Required Statistical Manipulations

Once all appropriate dose data have been normalized, the final step for completing all required calculations is to summarize the results for each specific job function or activity of concern. These calculations must be completed using the normalized values for each job function or activity monitored in a study and for data pertaining to each toxicologically significant chemical of interest (e.g., parent compound, metabolites, and manufacturing contaminants). The following statistical manipulations of the data should be completed:

- Arithmetic and geometric means for all test replicates based on the exposure route (e.g., dermal, inhalation);
- Standard deviations (σ) for all test replicates based on the exposure route;
- Number of replicates per calculation (N) and rationale for excluding any replicates; and
- Coefficients of variation for all test replicates based on the exposure route (Eq. D2-1).

Because values within many groups of data are distributed lognormally rather than normally, geometric statistical parameters are required along with the arithmetic mean (etc.). As a guide, if the standard deviation approximates or exceeds the mean, data are generally distributed lognormally rather than normally. However, as an alternative, investigators may apply appropriate statistical tests to data to define distributions. Investigators must justify their test selections for distributional analysis (e.g., use of commercial software and test selection).

2.5 CHEMICAL DISSIPATION KINETICS

Several standard approaches can be utilized to identify and quantify mechanisms of chemical dissipation and degradation (e.g., 1st order, 2nd order, etc.). Historically, available data have indicated that dislodgeable foliar and soil residue dissipation over time may be modeled using pseudo-first order kinetics. The same observation appears to be true for other residue types (e.g., indoor surfaces and turf). Pseudo-first order kinetics are appropriate because determining the actual dissipation mechanism and defining how individual parameters affect dissipation/degradation are impractical considering the scope of the studies required under these guidelines.

The first objective for completing a kinetics analysis of chemical dissipation data is to ensure that the following calculations have been completed.

- Arithmetic means for all replicate samples for each sampling interval;
- Standard deviations (σ) for all replicate samples for each sampling interval;
- Number of replicates per calculation (N) and rationale for excluding any datapoints for all preliminary statistical calculations; and

- Coefficients of variation for all replicate samples for each sampling interval. (See Eq. D2-1.)

The next objective is to develop an equation that describes the chemical dissipation over time. In most cases, the Agency has observed that chemical dissipation data are lognormally distributed over time. Because values within many groups of data are distributed lognormally rather than normally, geometric parameters are required along with the arithmetic mean (etc.). Testing to determine whether data are normally or lognormally distributed is unreliable for small data sets. Therefore, the decision to assume lognormality is usually adopted, based on experience. The easiest approach for developing a linear equation to describe the data is to plot the data (i.e., typically the means for all replicate samples collected at each sampling interval) in a semi-log fashion after transformation of the chemical residue levels at each sampling interval. As a convention, the Agency prefers that natural logarithms (ln) of the chemical residues be plotted versus dissipation time (postapplication interval). After the plot of the data has been developed, a linear regression must be completed to determine if there is adequate correlation between the residue levels and time (postapplication intervals) to describe the chemical dissipation process using a linear equation. Environmental concentrations can be predicted using semi-log or log-linear regression residue dissipation equations of the form:

$$C_{envir(t)} = C_{envir(0)} e^{(PAI_{(t)} \cdot M)} \qquad \text{(Eq. D2-16)}$$

Where:

$C_{envir(t)}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at time (t), (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm);

$C_{envir(0)}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at time (0), (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm) (see Eq. D2-17 below);

e = the base of natural logarithms (i.e., 2.718281828...);

PAI_t = postapplication interval or dissipation time (t, usually hours or days); and

M = slope of line generated during linear regression of data [$\ln(C_{envir})$ versus PAI] (see Eq. D2-17 below).

By taking the natural logarithm of the C_{envir} at each sampling interval and regressing these values against the postapplication interval (PAI) that corresponds to the sample, the regression coefficients M and b can be derived using the linear equation:

$$\ln(C_{envir\,(t)}) = (M * PAI_{(t)}) + b \qquad \text{(Eq. D2-17)}$$

Where:

$C_{envir\,(t)}$ = environmental residue concentration (e.g., dislodgeable foliar residue) at time (t), (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm);

M = slope of line generated during linear regression of data [$\ln(C_{envir\,(t)})$ versus PAI];

$PAI_{(t)}$ = postapplication interval or dissipation time (t, usually hours or days); and

b = y intercept of the linear equation generated during regression of the ln ($C_{envir\,(0)}$).

A half-life ($t_{1/2}$) is a more intuitive expression of the slope (M) calculated above. In addition to the development of an equation that quantifies the chemical dissipation rate, calculation of $t_{1/2}$ for each analyte of concern should be completed using the following equation:

$$t_{1/2} = (-0.693/M) \qquad \text{(Eq. D2-18)}$$

Where:

$t_{1/2}$ = chemical half-life for dissipation data that represents the interval of time it takes for a chemical residue at time 0 to dissipate to 50 percent of the initial level (e.g., days or hours);

0.693 = constant calculated for this kinetics model (i.e., ln(2)); and

M = slope of line generated during linear regression of data [$\ln(C_{envir\,(t)})$ versus PAI].

Natural logarithmic (ln) transformations are required for calculation of the appropriate slope for the pseudo-first order kinetics model described above rather than common base 10 logarithms (log). A model of the form $C_{envir\,(t)} = C_{envir\,(0)}10^{(PAI * M)}$ would be equally valid, but the slope would need to be converted to a half-life via $t_{½} = -0.301/M_{log}$. Additionally, common software packages can be used to complete linear regression calculations. The name and version number must, however, be reported in any submission to the Agency.

The Agency recognizes that completion of a chemical kinetics analysis is often difficult. In a majority of cases, the approach outlined above provides an adequate basis for modeling dissipation of a chemical from treated surfaces and environmental matrices. However, in cases where pseudo-first order kinetics do not apply, other models may be used, including graphical techniques, if they are adequately explained and justified in any submission to the Agency (e.g., Gustafson and Holden, 1990).

2.6 TRANSFER COEFFICIENTS AND EXPOSURE MODELS

The Agency's long-term objective for requiring concurrent postapplication human exposure and chemical dissipation data is to establish a data base of transfer coefficients for specific activities in order to calculate the risk or hazard at other times with other residue levels. Transfer factors quantitatively establish the relationship between activity, chemical concentrations in the environment, and dose. The purpose of transfer coefficients is to calculate dose levels when no appropriate human monitoring data are available (i.e., they provide a mechanism for predicting dose levels when only environmental concentration data are available and they provide a basis for ranking the relative dose levels associated with various activities).

2.6.1 Calculation of Transfer Coefficients

The calculation of transfer coefficients involves relating measured doses to concurrently measured chemical concentrations in environmental media. Transfer coefficients should be representative of particular activities including: harvesting and maintaining particular crops; handpacking commodities; or indoor and outdoor residential activities. It should be noted that transfer coefficients typically have only been applied to the dermal exposure route. However, the concept is sound for other exposure routes (e.g., inhalation or nondietary ingestion). When the main source of exposure is via inhalation, dermal transfer coefficients cannot be used to estimate potential bystander exposure and an exposure study should be conducted. The equation below provides an example of the calculation of a transfer coefficient for the dermal exposure route as it is the most commonly route used for of the concept:

$$TC = (D_{dermal}/C_{envir}) \qquad \text{(Eq. D2-19)}$$

Where:

TC = residue transfer rate to humans during the completion of specific activities, calculated using concurrently collected environmental data; environmental data may be actual or predicted based on a kinetics analysis of the data--investigators must justify their selection (e.g., cm^2/hr);

D_{dermal} = dermal dose (e.g., typically μg or mg/hour); and

C_{envir} = environmental residue concentration (e.g., dislodgeable foliar residue) at the time concurrent to the dermal exposure, (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm).

[NOTE: The chemical mass in D_{dermal} and C_{envir} must be expressed in the same units for the equation above to be appropriate.]

The transfer coefficient described above is a simple proportion that compares dermal dose to a chemical concentration (i.e., it assumes that the relationship is linear between dose and environmental chemical concentration over time and with fluxuation in the environmental chemical concentration). More sophisticated techniques that may account for variability in the relationship between dose levels and residue levels may also be utilized. For example, as an alternative to point estimates, investigators may wish to consider using the empirical distribution of transfer coefficient data for use in probabilistic assessments. The following are alternative suggestions for quantitatively representing chemical transfer on a job or activity specific basis:

- Develop linear equations that describe the relationship between dose and environmental residue level (e.g., semilog plot of D_{dermal} vs. C_{envir}); and
- Investigate calculating transfer coefficients based on other aspects of a test subject's activity such as efficiency (e.g., pounds fruit harvested).

Investigators must calculate transfer coefficients for every study that contains concurrent environmental chemical concentration and dermal dose data. Transfer coefficients must be calculated for every job function that is monitored in a study. Investigators may use whichever technique they feel is appropriate for calculating transfer coefficients. However, all calculations must be clearly documented and the use of any statistical tests must be referenced and justified in submissions to the Agency.

2.6.2 Use of Transfer Coefficients

Transfer coefficients (TC) are used to calculate dose levels using an environmental chemical concentration when no concurrent human exposure monitoring data are available (i.e., they provide a surrogate basis for calculating dose levels). Where possible, actual monitoring data as well as dose levels predicted using the TC value should be presented by investigators for comparison by the Agency. The basic premise of the TC approach is generally considered valid for all dermal exposure scenarios including adults engaged in occupational activities and sensitive populations in a residential setting. The Agency is engaged in a research effort that will establish a quantitative basis or predicting exposures to sensitive populations (i.e., defining the extrapolation process from adult test subjects to a sensitive population). In other words, the TC in conjunction with the C_{envir} replace the contaminant concentration (C) and contact rate (CR) terms in the equations that describe dose and average daily or lifetime average daily dose (ADD or LADD). (See Eq. D1-3 for further information.) The basic equation for using transfer coefficients is provided below:

$$D_{dermal} = TC * C_{envir} \qquad \text{(Eq. D2-20)}$$

Where:

D_{dermal} = total dermal dose (e.g., μg or mg/hour);

TC = residue transfer rate to humans during the completion of specific activities (e.g., cm^2/hour); and

C_{envir} = concentration of residue in an environmental matrix such as dislodgeable foliar residue (μg or mg/cm^2), in soil (ppm) or indoor surface residue data (μg or mg/cm^2).

For defining a limit of detection/limit of quantification (i.e., until a specific factor for the activities of interest is generated) a transfer coefficient of 10,000 cm^2/hr should be used as a surrogate value where no appropriate data exist.

2.6.3 Currently Used Assumptions for Assessing Nondietary Ingestion Exposure

As an interim measure, the Agency has developed approaches for addressing nondietary ingestion exposure to toddlers and small children. Nondietary ingestion can occur from hand-to-mouth transfer or direct ingestion of chemicals or chemically treated materials found in the environment. Equations for addressing each scenario are presented below based on the exposure pathways of critical concern to the Agency:

Hand-to-mouth transfer

Nondietary ingestion dose attributable to hand-to-mouth activity includes several scenarios (e.g., smoking with contaminated hands after harvest, exposure to infants after crawling on treated turf). Equation D2-21, presented below, addresses how nondietary ingestion dose due to hand to mouth contact can be calculated.

$$D_{HMI(t)} = C_{envir} \times HSA \times F \times CFI \times ET \qquad \text{(Eq. D2-21)}$$

Where:

$D_{HMI(t)}$ = nondietary ingestion dose attributable to hand to mouth activity at time (t) after chemical application (mg/day);

C_{envir} = environmental residue concentration (e.g., turf dislodgeable foliar residue) at time (t), (units are sampling/matrix dependent, typical units are $\mu g/cm^2$ or ppm);

HSA = human skin surface areas for body parts of interest (cm^2/body part);

F = frequency of hand-to-mouth events (events/min);

CFI = time unit conversion factor (60 min/hr); and

ET = exposure time (hours/day).

[Note: Please refer to the U.S. EPA Exposure Factors Handbook for data pertaining to skin surface areas (U.S. EPA, 1996).]

Foreign object/matter nondietary ingestion exposure

Nondietary exposure attributable to the ingestion of foreign objects or matter laden with chemical residues from a previous application can represent several pathways (e.g., ingestion of soils, turf, and paint chips). Equation D2-22, presented below, addresses how dose attributable to the ingestion of foreign matter/objects laden with chemical residues can be calculated.

$$D_{NDI(t)} = IgR \times WF \times CFI \qquad \text{(Eq. D2-22)}$$

Where:

$D_{NDI(t)}$ = nondietary ingestion dose attributable to ingestion of chemical residue laden materials at time (t) after chemical application (mg/day);

IgR = ingestion rate of foreign objects/materials (g/day);

WF = weight fraction of a chemical residue contained on foreign matter/objects that are ingested (unitless); and

CFI = weight unit conversion factor to convert gram units in the ingestion rate value to mg for the daily exposure (1,000 mg/g).

2.6.4 Swimmer Exposure

Swimmer exposure is a unique reentry scenario that is based on the premise of total absorption into the body via seven routes (Dang, 1996). These seven routes are: oral, dermal, inhalation, buccal/sublingual, orbital/nasal, aural, and via male sexual organs. Generally, the oral, dermal, and inhalation exposure routes contribute predominantly to a swimmer's overall dose resulting from exposure to pool treatment chemicals. Equations D2-23 through D2-29 document the Agency approach for calculating oral (nondietary ingestion), dermal, and inhalation doses to swimmers.

Nondietary ingestion (oral) doses to swimmers can be calculated as follows:

$$D_{\text{int.ing (swim)}} = C_w * IgR * ET \qquad \text{(Eq. D2-23)}$$

Where:

$D_{\text{int.ing (swim)}}$ = nondietary ingestion dose attributable to oral intake of pool water while swimming (mg/day);

C_w = chemical concentration in pool water (mg/L);

IgR = ingestion rate of pool water (L/hour); and

ET = exposure time (hours/day).

C_w can either be measured, predicted (i.e, based on the chemical-specific data pertaining to the environmental fate characteristics of the chemical), or approximated as follows:

$$C_w = AR * CF1 * CF2 \qquad \text{(Eq. D2-24)}$$

Where:

AR = application rate of active ingredient (e.g., lbs ai/gal);

CF1 = weight unit conversion factor (4.54E5 mg/lb); and

CF2 = volume unit conversion factor (2.64E-1 gal/L).

Internal dermal doses to swimmers can be calculated as follows:

$$D_{\text{int.derm. (swim)}} = C_w * HSA * ET * K_p * CF1 \qquad \text{(Eq. D2-25)}$$

Where:

$D_{\text{int.derm. (swim)}}$ = internal dermal dose attributable to swimming in treated pool water (mg/day);

C_w = chemical concentration in pool water (mg/L) (see Eq. D2-24 above);

HSA = human skin surface areas for body parts of interest (cm^2/body part);

ET = exposure time (hours/day);

K_p = dermal permeability coefficient (cm/hr); and

CF1 = volume unit conversion factor (L/1,000 cm^3).

[Note: See Exposure Factors Handbook for data pertaining to skin surface areas (U.S. EPA, 1996).]

Inhalation exposures to swimmers can be calculated as follows:

$$D_{\text{int.inh (swim)}} = C_{vp} * IR * ET \qquad \text{(Eq. D2-26)}$$

Where:

$D_{\text{int.inh (swim)}}$ = internal inhalation dose attributable to swimming in treated pool water (mg/day);

C_{vp} = vapor concentration of chemical in air (mg/m^3);

IR = inhalation rate (m^3/hour); and

ET = exposure time (hours/day).

C_{vp} may be calculated as follows (Dang, 1996):

$$C_{vp} = \frac{(C_w * VP * 273\ K * MW * 1{,}000\ L/m^3 * L/1{,}000\ g)}{(760\ mm\ Hg * T * 22.4\ L/mole)} \qquad \text{(Eq. D2-27)}$$

Where:

C_w = concentration of ai in water (mg/L);

VP = vapor pressure (mm Hg or Torr) at the pool water temperature (see Eq. D2-24 above);

T = Kelvin temperature (K); and

MW = molecular weight of water (18 g/mole).

[Note: See Exposure Factors Handbook for data pertaining to human inhalation rates (U.S. EPA, 1996). Dang (1996) also provides information pertaining to the inhalation rates of swimmers.]

2.7 AVERAGE DAILY DOSE

Generally, the calculation of an ADD value is required for all hazard or risk assessments. Investigators must determine, based on the route of administration of the toxicological endpoint of concern, whether the ADD_{pot} or ADD_{int} should be calculated. For example, if the endpoint is based on a 21-day dermal subchronic study, the ADD_{pot} should be used. In all cases, as a matter of convention, ADD_{pot} values will be used to represent dose levels that have been adjusted by body weight and the hours spent in each activity. However, if the endpoint is based on an oral administration of test material, ADD_{int} should be calculated (i.e., a dermal absorption factor must be applied to the ADD_{pot}; 100 percent is generally assumed if no actual data are available). Additionally, investigators must determine, based on the toxicological endpoint, if any further calculations are required prior to the calculation of the hazard or risk. If the endpoint is acute or subchronic (i.e., less than lifetime), no further calculations are required. If the endpoint is cancer, calculation of the LADD may be also required. (See below.) The equation that can be used to calculate ADD values is presented below:

$$ADD_{pot\ or\ int} = ((D_{unit} * AdF)/BW) \qquad \text{(Eq. D2-28)}$$

Where:

$ADD_{pot\ or\ int}$ = average daily $dose_{pot\ or\ int}$ which is calculated based on the D_{unit} and the appropriate adjustment factors (e.g., μg or mg/kg body weight/8 hour day);

D_{unit} = unit dose (potential or internal) calculated using ?????(e.g., μg/hour) (Eq. D2-15);

AdF = adjustment factor which replaces the quotient [(CR*ED*F)/AT] described in the general equation of ADD included in Chapter 1 of part D. This adjustment factor may be based on, but not limited to, the following: time (e.g., hours at work or in residence), the amount harvested (e.g., pounds picked), or amount maintained (e.g., acres mowed), [Note: this factor must be congruous to the normalization factor used to calculate the D_{unit}]; and

BW = body weight value used to normalize the ADD value (kg). Investigators must be careful to determine the appropriate value based on the population at risk (e.g., adults, infants, toddlers, etc.). [Note: See Exposure Factors Handbook (U.S. EPA, 1996) for most recent guidance pertaining to the selection of a proper body weight value.]

As indicated above, the ADD_{pot} or ADD_{int} is typically used for noncarcinogenic chemicals (i.e., the exposures of concern are of an acute or subchronic nature). If the endpoint is cancer, the ADD must be amortized over the duration of a lifetime using the calculation for a LADD. An equation that can be used to calculate LADD values is presented below:

$$LADD_{Pot\ or\ Int} = ADD_{Pot\ or\ Int} * (F/365) * (ED/LT)) \qquad \text{(Eq. D2-29)}$$

Where:

$LADD_{Pot\ or\ Int}$ = $ADD_{Pot\ or\ Int}$ amortized over an individual's lifetime (e.g., mg/kg/day);

$ADD_{Pot\ or\ Int}$ = see (Eq. D2-28) above;

F = frequency of exposure events or the number of days exposed to the pesticide of concern per annum (days/year);

ED = exposure duration throughout a lifetime or the number of years exposed to a specific chemical throughout an individual's lifetime (years); and

LT = anticipated lifetime of an individual in the exposed population of interest (years), investigators must be careful to determine the appropriate value based on the population at risk (e.g., males or females).

The inputs that are selected and used by investigators must be documented for each specific chemical use scenario of concern. Default parameters should be based on standard reference sources such as the Agency's Exposure Factors Handbook (U.S. EPA, 1996) and the Risk Assessment Guide for Superfund (U.S. EPA, 1988). Investigators are encouraged to consult the Agency regarding these types of calculations.

2.8 HAZARDS, RISKS, AND RESTRICTED ENTRY INTERVALS

The calculation of hazards or risks resulting from reentry exposure are addressed in this section. Fundamentals and risk assessment are addressed in Part D, Chapter 1. This section addresses specific applications of those principles (i.e., calculation of restricted-entry intervals for commercial, industrial, and agricultural uses of pesticides and determination of hazard/risk levels in residential settings). With the 1996 passage of the Food Quality Protection Act, investigators are cautioned to consider the new elements of the risk assessment process (e.g., aggregate risk). As such, note that the requirements for residential exposure assessment are much more involved than they have been historically. These requirements are described below as appropriate.

Carcinogenic risks may be calculated as described in Part D, Chapter 1. Calculations are based on LADDs due to the non-threshold nature of carcinogenic risk and are only appropriate when a cancer slope factor is available (i.e., cancer is the endpoint of concern). Risks from postapplication exposures are calculated using the following equation:

$$R = LADD_{\text{Pot or Int}} * (SF) \qquad \text{(Eq. D2-30)}$$

Where:

R = risk which represents the probability of excess cancer cases over a lifetime as described in Part D/Chapter 1 (unitless);

$LADD_{\text{Pot or Int}}$ = described above in (Eq. D2-29); and

SF = cancer slope factor for the chemical of interest $(mg/kg/day)^{-1}$.

Hazard assessment can be based on a variety of toxicological endpoints. As described in Chapter 1 of Part D, a hazard quotient represents the ratio of the calculated dose to the toxicological endpoint expressed as a reference dose or concentration. If the hazard quotient is greater than one, an effect would be expected; however, if the ratio is less than one, no effects would be expected. Hazard quotients are not a probabilistic statement of risk. Based on the common approach utilized by the Agency, noncarcinogenic hazards are also be represented as the Margin of Exposure (MOE). This approach is more common because of the lack of RfD/RfC values for various chemicals. MOE is the ratio of a NOAEL or LOAEL to a dose level. High MOEs (i.e., > 100) imply a low level of concern. As the MOE decreases, the level of concern increases. Neither MOEs nor hazard quotients are a probabilistic statement of risk. MOEs, regardless of the endpoint, can be calculated using the following equation:

$$MOE = TE/(ADD_{Pot\ or\ Int}) \qquad \text{(Eq. D2-31)}$$

Where:

MOE = margin of exposure which reflects the ratio of toxicological endpoint to chemical dose, the level of concern increases as the ratio approaches 0, values approaching 100 or more indicate that concern is negligible for a particular exposure scenario (unitless);

TE = toxicological endpoint which quantitatively represents the biological effect caused by exposure to a chemical (e.g., NOAEL/LOAEL for acute or subchronic data); and

ADD = $ADD_{Pot\ or\ Int}$-based on the descriptions provided above in (Eqn. D2-28).

2.8.1 Restricted Entry Interval (REI) Scenarios

Restricted Entry Intervals (REIs) represent the time interval after pesticide application that it takes for resulting residues to dissipate to a level at which human reentry into the treated area would pose a negligible hazard or risk. REIs are used as a tool by the Agency to minimize the risks by altering labels to include the calculated REIs. REIs are generally required only for the completion of assigned tasks in settings where regulation of a chemical via the implementation of an REI is appropriate (e.g., occupational exposure scenarios for agricultural, commercial, and industrial settings). In some cases, the implementation of an REI is inappropriate. For example, for chemicals applied to residential turf, an unacceptable acute hazard is never appropriate (i.e., to allow time for chemical dissipation). Therefore, a different approach must be used for scenarios where the REI is inappropriate. (See Section 2.8.2 below for details.)

Historically, the Agency has used two distinct techniques for the determination of REIs: (1) the nondetectable residue method, and (2) the Reentry Dose Level (RDL) method. The nondetectable residue method entails the identification of the postapplication interval at which residue levels become nondetectable regardless of the quantification or detection limits of the analytical methodologies. This approach is no longer recommended because, for many chemicals, even when one-half of the quantification or detection limits are utilized in the calculations, there is an unacceptable hazard or risk level associated with the exposure scenario.

The RDL method calculates a dose level for reentry that is below a biological threshold. This is accomplished by the application of a safety factor or series of safety factors to the appropriate toxicological endpoint. The generic equation below illustrates the concept:

$$RDL = TE / SF \qquad \text{(Eq. D2-32)}$$

Where:

RDL = reentry dose level or level at which reentry into an area previously treated with a chemical can occur with negligible deleterious effects caused by exposure to the chemical because the biological mode of action threshold for that chemical has not been met (e.g., mg/kg/day);

TE = toxicological endpoint which quantitatively represents the biological effects caused by exposure to a chemical such as the NOAEL/LOAEL for acute or subchronic data (e.g., mg/kg/day); and

SF = safety factor, based on the nature of the toxicological endpoint, that is used to extrapolate the available toxicological database to the appropriate exposure route of concern in humans (e.g., 10 for interspecies correlation) and to set an appropriate MOE cutoff value (unitless).

After the RDL is established, an Ambient Reentry Concentration (ARC) is determined by comparing the dose level to the appropriate chemical dissipation data (e.g., plot of DFR levels vs. corresponding dose levels) as illustrated in Figure D2-3. The process can be completed using a graphical procedure or an algorithm that relates residue and dose levels or an algorithm may be developed that relates residue and dose levels (e.g., Eq. D2-19). It should be noted that the ARC which

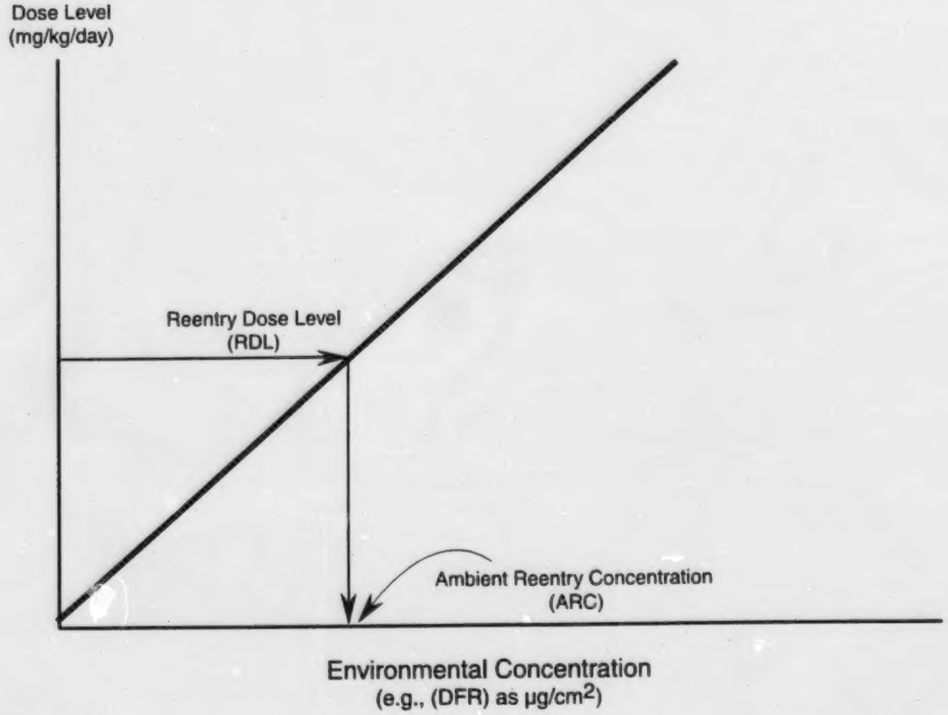

Dose Level
(mg/kg/day)
Reentry Dose Level
(RDL)
Ambient Reentry Concentration
(ARC)
Environmental Concentration
(e.g., (DFR) as µg/cm2)

Figure D2-3. Determination of an ARC Using the RDL Method

corresponds to the RDL is dependent on the slope of the line depicted in Figure D2-3. That line is generated from empirical studies in which dislodgeable foliar residues and dermal exposure measurements were collected simultaneously. Essentially, the line represents the transfer coefficient, and is specific to crop activity, and pesticide. The slope of the line will differ depending on differences in one or more of these factors.

Finally, the REI is calculated. The REI represents the interval required for chemical residues to dissipate to the ARC. This determination is made by comparing residue dissipation data to the postapplication interval (e.g., plot of $\ln(C_{envir})$ versus PAI). This process is illustrated in Figure D2-4. The process can be completed using a graphical procedure or an algorithm that relates C_{envir} and the PAI. It should be noted that not all residues are anticipated to decay exponentially. As result, data needs to be modeled appropriately so that an REI can be calculated (e.g., biphasic dissipation).

The application and scope of the calculations described above are similar regardless of the exposure scenario or the sampling protocol (e.g., concurrent residue dissipation and exposure data will be treated in similar fashion regardless of where the data were generated -- agricultural, commercial, or industrial). The Agency recognizes that study and chemical specific adjustments may be required. Investigators must be careful to clearly document any major deviation from the required calculation strategies. It should be noted that several issues exist concerning variability and uncertainty related to the calculation of REIs that eventually must be addressed by the Agency. These issues include the relationship between residue levels and transfer coefficients, selecting appropriate dissipation models, and the calculation of exposure data.

2.8.2 Non-REI Scenarios

Calculation of REIs is not appropriate for residential use chemicals as well as a variety of other exposure scenarios where the implementation of an REI may not be feasible (e.g., antimicrobial uses in swimming pools and indoor applications, etc.). Reentry into chemically treated residential areas must be possible on the day of application. The Agency must also consider the only acceptable REI to be the day of application for chemicals with acute endpoints. To determine whether reentry into treated residential areas on the day of chemical application is safe, the procedure for calculating REIs is reversed. First, the ARC on the day of application is determined. Next, the dose level corresponding to that particular ARC is determined based on the equations and guidance presented above in Section 2.8.1. This dose level is then compared to the RDL to determine if humans are adequately protected from adverse effects associated with reentry exposure. (See Figures D2-3 and D2-4 for further information.) The process too can be completed using a simple graphical procedure or an algorithm may be developed that relates residue and dose levels.

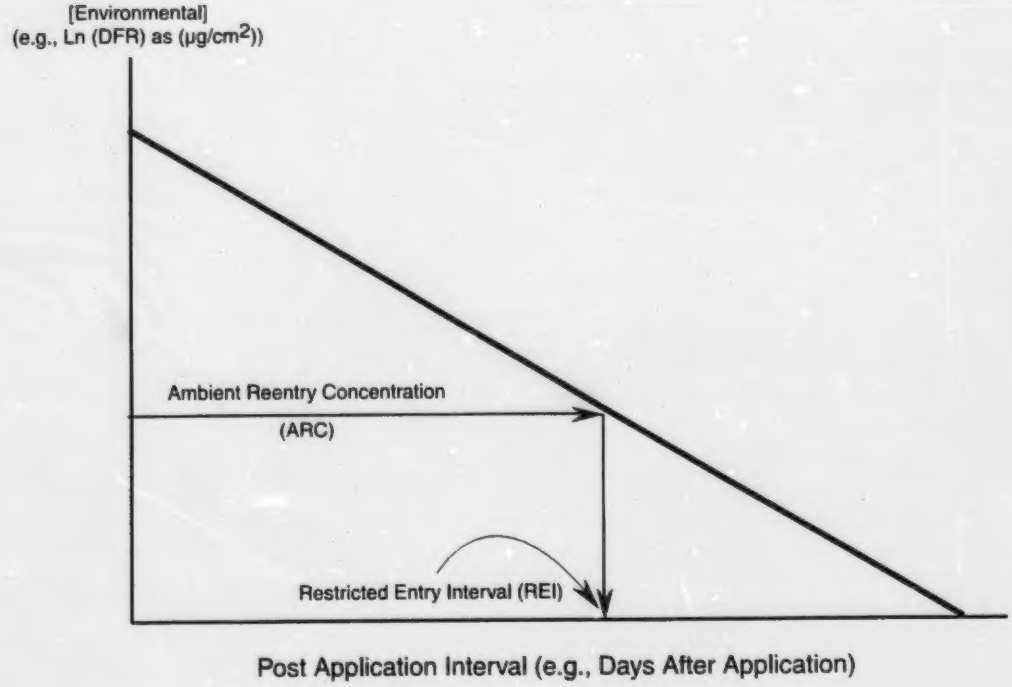

[Environmental]
(e.g., Ln (DFR) as (µg/cm2))
Ambient Reentry Concentration
(ARC)
Restricted Entry Interval (REI)
Post Application Interval (e.g., Days After Application)

Figure D2-4. Determination of an REI Using the ARC Method

With the enactment of the Food Quality Protection Act (FQPA), the Agency must now also complete aggregate hazard or risk assessments. In particular, this concept applies to residential and nonoccupational exposure scenarios where subchronic and chronic toxicological endpoints have been identified. Historically, the Agency's approach for residential exposure assessment was based on whether or not a single chemical use pattern was "safe" directly after the application. However, in the aggregate risk approach, the Agency must now consider risks associated with multiple use patterns for a chemical even if the use patterns, when considered individually, would be considered acceptable on the day of application. Assessors must calculate risks or hazards from non-REI exposure scenarios until the chemical dissipation reaches the limit of quantification using chemical specific exposure data or surrogate TC values (i.e., calculate exposures for the chemical dissipation curve until the curve reaches the LOQ). The calculated exposures for each scenario must then be summed to calculate aggregate risk.

Several uncertainty and variability issues also exist for non-REI scenarios in addition to those noted above in Section 2.8.1. Dose is a function of exposure, and exposure is a function of environmental concentration and activity pattern. Unless the activity pattern is defined, the dose level associated with an environmental concentration and population of concern cannot be defined. In occupational exposure assessment, transfer coefficients for specific work functions generally define the daily activity pattern. However, the activity patterns for residential scenarios are more difficult to define as they involve different demographic groups (e.g. infants, toddlers, adults) involved in different activities (e.g., walking, crawling, etc.).

2.9 EXAMPLE CALCULATIONS

Example calculations are provided in this section that illustrate the general use of the equations presented in sections D2.2 through D2.8 using a hypothetical dataset. This section follows the format of the previous sections. For the purposes of this section, an example has been developed based on an agricultural reentry scenario. However, the same principles can be applied to residential, industrial, and commercial scenarios. Any values or data presented in this section should not be construed as default values or representing Agency policy. They are presented strictly for illustrative purposes. A series of tables are presented that include example data. A parameter is included in these tables that is called "Line Number." This parameter is intended to provide a mechanism for tracking data throughout the example.

2.9.1 Example Scenario

The example calculations in this section are based on the following parameters:

- *Exposure Monitoring Techniques:* whole body dosimeters (thermal underwear pants and long-sleeved tee-shirts covering the upper and lower body under normal work clothing -- long pants and long sleeves), handwashes collected twice per interval, inhalation monitoring using personal sampling pumps, and head exposure using two 100 cm^2 patches;

- *Exposure Monitoring Regimen:* 15 replicates of citrus thinning were completed on 3 separate days after application (i.e., days 1, 2, and 4 after application);

- *Application Scenario:* an insecticide was applied using an airblast sprayer to citrus 1 day prior to thinning; the example pesticide can also be applied in a residential scenario (a single application scenario is included, multiple application scenarios require assessing accumulation between applications);

- *Dislodgeable Foliar Residue Monitoring:* 5 replicate samples were collected at each sampling interval starting prior to application (i.e., baseline), after application (the sprays have dried), and on the following days after application: 1, 2, 4, 7, 10, 14, 21, 28, and 35;

- *Quality Control:* Recovery samples were generated in the field for each sampling media as appropriate; all recovery samples were collected, shipped, stored, and analyzed concurrently with field samples -- the recovery data represent field and laboratory recovery as well as storage stability;

- *Toxicological Endpoints:* exposure and hazard/risk scenarios are presented for a short-term and a cancer endpoint; the factors used in the example calculations include a percutaneous absorption factor of 15 percent, a 21 day dermal rat study with a NOEL of 10 mg/kg/day, a cancer slope factor of 1×10^{-2} (mg/kg/day)$^{-1}$, and a body weight of 70 kg; and

- *Exposure Calculation Scenarios:* daily work intervals will be 8 hours and lifetime average daily amortization factors for cancer endpoints will be a 70 year lifetime and a 35 year working lifetime.

2.9.2 Commonly Used Formulas and Approaches

This section provides examples of the appropriate use of common formulas/approaches discussed in Section D2.2. The sample raw data to be used for these calculations are presented in

Table D2-1. The appropriate use of quantification/detection limits is also presented in this table. For the purposes of this example the quantification limit is the lowest fortification level specified for each matrix and the detection limit is 5x lower for each matrix. "NQ" indicates that the residue level was greater than the LOD but less than the LOQ. "ND" indicates the residue level was less than or equal to the LOD.

2.9.3 Chemical Data

Example quality control data are also presented in Table D2-1 and a summary of these data are presented in Table D2-2. The use of basic statistical formulas is also described in Table D2-2. The summary table illustrates how quality control data should be analyzed and presented in any submission to the Agency. The summary table includes the calculation of means, standard deviations (σ), coefficients of variation, and confidence intervals for each fortification level and over all fortification levels.

After all quality control data are summarized, the next step is to develop unit values (i.e., normalize) for all exposure and environmental data. For example, raw analytical data are generally presented as (μg/sample) values. If the data are Iwata-type dislodgeable foliar residues, the (μg/sample) values have to be normalized based on the double-sided leaf surface area of the sample (i.e., using a 2.5 cm diameter leaf punch for the purposes of this example). Normalization is completed by dividing the residue level by the surface area. In cases where a leaf punch device is not appropriate (e.g., pine needles), the leaf area for each sample must be calculated using a surface area to weight factor. Examples of both of these types of calculations are provided in Table D2-3. Additionally, human exposure monitoring data sometimes require normalization. For dermal patches, this normalization process is analogous to the process for the use of a leaf punch device (i.e., refer to Table D2-3 for guidance). For air monitoring data, the process differs in that the calibration of the air sampling device must be addressed and a volume must be calculated which is used to normalize the measured residue level. An example air calculation is presented in Table D2-4.

After all human exposure and environmental data are normalized, the quality control data should be assessed to determine if correction of the raw residue data are required based on the results of the quality control regimen. Generally, the Agency requires that data be corrected if the recovery correction factor calculated for the dataset is less than 90 percent. In this example, the recovery data presented in Table D2-1 and summarized in Table D2-2 represent the simplest scenario for developing a recovery correction factor. All data presented in the example are assumed to have been generated in the field with

Table D2-1. Raw Data (Day 2) to be Used in Example Calculations

Line	Field Recovery[a] Whole Body Dosimeters		Upper Torso Dermal Exposure Using Whole Body Dosimeters[c,d] (not recovery corrected) (μg/sample)	Field Recovery[a] Dislodging Solutions		Dislodgeable Foliar Residues[b,c] (not recovery corrected) ($\mu g/cm^2$)
	Fortification Level (μg/sample)	Recovery (%)		Fortification Level (μg/sample)	Recovery (%)	
1	10.0	69.5	15.0	2.0	68.0	0.8400
2	10.0	85.5	205	2.0	65.0	0.6500
3	10.0	86.0	NQ	2.0	71.0	NQ
4	10.0	65.0	1236	2.0	74.0	0.5800
5	10.0	71.0	115	2.0	67.0	0.6000
6	100.0	72.0	19.0	100.0	110	N/A
7	100.0	78.0	550	100.0	89.0	N/A
8	100.0	89.0	89.0	100.0	75.0	N/A
9	100.0	112.0	ND	100.0	70.0	N/A
10	100.0	69.0	55.0	100.0	81.0	N/A
11	1000.0	110.0	68.0	1000.0	71.0	N/A
12	1000.0	108.0	601	1000.0	112	N/A
13	1000.0	89.0	428	1000.0	83.0	N/A
14	1000.0	81.0	292	1000.0	69.0	N/A
15	1000.0	84.0	19.0	1000.0	73.0	N/A

a Field recovery for whole body dosimeter and dislodging solution samples will serve all analytical functions in this example except where noted (i.e., samples are assumed to have been field recovery samples that were shipped, stored and analyzed concurrently with the field samples -- they will also act as laboratory recovery and storage stability data).

b Dislodgeable foliar residue samples represent a double-sided leaf surface area/sample of 400 cm^2. The DFR levels presented in this table represent data collected from a site 2 days after application and concurrently with the whole body dosimeter data also presented in this table. Additionally, a total of 5 replicate DFR samples are assumed to have been collected at this sampling interval and that the field recovery data for this study were generated on this sampling day.

c For the purposes of this example, the limit of quantification (LOQ) will be considered the lowest sample fortification level presented above for each matrix (i.e., 10.0 μg/sample for dosimeters and 2.0 μg/sample or 0.005 $\mu g/cm^2$ for the dislodgeable residue samples). Likewise, for the purposes of this example, the limit of detection (LOD) will be considered 5x lower than the LOQ for calculation purposes. "ND" and "NQ" represent the following: NQ = residue level X if $LOD < X < LOQ$; ND = residue level X if $X \leq LOD$.

d For the purposes of further calculations, the whole-body dosimeter levels presented in this table represent only the upper torso of monitored individuals (i.e., long-sleeved tee-shirts were assumed to have been used as the monitor).

Table D2-2. Summary Statistics for Example Field Recovery[a]

Fortification Level (µg/sample)	**Whole Body Dosimeter Field Recovery**				**Dislodgeable Foliar Residue Solution Field Recovery**			
	Mean[b] (%)	**σ[b] (%)**	**C.V.[c]**	**95% CI[d] (%)**	**Mean[b] (%)**	**σ[b] (%)**	**C.V.[c]**	**95% CI[d] (%)**
10.0	75.4	9.70	12.9	66.9/83.9	69.0	3.54	5.1	65.9/72.1
100.0	84.0	17.42	20.7	68.7/99.3	85.0	15.67	18.4	71.3/98.7
1000.0	94.4	13.65	14.5	82.4/106.4	81.6	17.83	21.9	66.0/97.2
All Levels	84.6	15.22	18.0	76.9/92.3	78.5	14.67	18.7	71.1/85.9

[a] Data summaries in this table are based on the raw data presented in Table D2-1. Each fortification level represents 5 recovery samples (i.e., all data assumed to be generated on Day 2 of example as indicated in Table D2-1).

[b] Mean and σ values calculated using routines provided in a handheld calculator.

[c] C.V. = coefficient of variation calculated as described in Eq. D2-1 (12.9 = (9.70/75.4)*100)

[d] 95% CI = 95% confidence interval lower/upper limits calculated as described in Eq. D2-2 (66.9 = 75.4 - ((9.70 * 1.96)/√5))

Table D2-3. Example Day 2 Environmental Data Normalization

Table D2-1 Data Line	Required Data		
	Residue Level[a] (μg/sample)	**Sample Surface Area[b] (cm^2/sample)**	**Residue Level[a] (μg/cm^2)**
1	336.0	400	0.8400
2	260.0	400	0.6500
3	ND[c]	400	0.0005
4	232.0	400	0.5800
5	240.0	400	0.6000

a Residue levels (μg/sample) are not corrected for recovery.

b Surface area (400 cm^2) represents a sample that includes forty 1 inch diameter leaf punches where each leaf punch has a double-sided surface area of 10cm^2 ((πr^2) * 2). In the event that, if the leaf punch apparatus could not be used for sampling the particular crop, sample surface areas could be calculated using a pre-dislodging sample weight and a numerical relationship of sample weight to double-sided surface area as illustrated below (see Eqs. D2-3 through D2-5).

$$400 \text{ cm}^2 = (20 \text{ cm}^2/\text{gram plant material}) * (20 \text{ grams plant material/sample})$$

If a linear regression rather than a unit estimate is used for the calculation a simple linear equation would be developed rather than the above equation using the slope and intercept of the line.

c The assumed value for ND at one-half of the LOD is 0.2 μg/sample based on the detection limit being 5x lower than the LOQ of 2.0 μg/sample (i.e., 20 μg/(5 x 2) - 0.2 μg).

Table D2-4. Example Day 2 Air Data Normalization[a]

Line Number	**Required Data**						**[Air][c] (μg/m³)**
	Residue Level[a] (μg/sample)	**Personal Sampling Pump Operating Parameters[b]**					
		Exposure Interval (minutes)	**Initial Flow (Lpm)**	**Final Flow (Lpm)**	**Average Flow (Lpm)**	**Sample Volume (m³)**	
1	10.0	230	2.00	1.90	1.95	0.449	22.3
2	12.0	240	2.00	2.00	2.00	0.480	25.0
3	5.0	250	2.00	2.10	2.05	0.513	9.7
4	8.0	240	2.00	1.90	1.95	0.468	17.1
5	9.0	230	2.00	2.00	2.00	0.460	19.6

a All data included in this table have not been excerpted from the previous tables. Residue levels (μg/sample) are considered corrected for recovery for these example calculations. All data lines are not included in example for clarity.

b Lpm = liters per minute. Sample volume calculated using a conversion factor of (1m³/1000 liters) and the following equation (see Eq. D2-10):

Volume (m³) = Interval (min) * Average Flow (Lpm) * (1 m³/1000 liters)

c [Air] = Residue Concentration in air. This concentration calculated using the following equation (see Eq. D2-10):

[Air] (μg/m³) = Residue Level (μg/sample)/Sample Volume (m³) the exposure and environmental samples then transported, stored, and analyzed concurrently with the field samples. Therefore, the summarized recovery data are the appropriate correction factors because they represent field and travel recovery, storage stability, and concurrent laboratory recovery. An example correction factor calculation and associated data correction are presented in Table D2-5.

2.9.4 Dose Calculations

This section provides examples of human dose level calculations for passive dosimetry-based monitoring as discussed in Section D2.4. Specifically, potential dose, internal dose, unit dose, and required statistical calculations are presented for a scenario that is representative of the calculations required in this guideline. The basis for this example will be the use of passive dosimetry. For the purposes of this example, the monitored test subjects were assumed to be monitored using whole-body dosimeters (long-sleeved shirt and thermal underwear pants), handwashes (both combined for analysis), head patches (one on front and one on back), and personal sampling pumps for inhalation. In this example, two sets of hand wash samples and one set of all other samples were generated over each exposure replicate because each test subject was assumed to have taken a restroom break during the middle of the exposure interval. Examples are not presented for biological monitoring because the use of biological monitoring techniques is less common (due to a lack of adequate chemical-specific pharmacokinetic data), investigators are encouraged to contact the Agency regarding calculations and the appropriate presentation of these types of data.

The first step of the process is to calculate potential dose as described in Section D.2.4.1. In this example, whole body dosimeters and patches are used to illustrate nonhand dermal dose. The surface area of each patch was assumed to be 100 cm^2. Patch samples were combined for analysis, therefore, the head sample surface area was 200 cm^2. Calculation of total dermal dose is the first requirement as described in Eqs. D2-8 and D2-9. In order to calculate total dermal dose, the head patch value must be adjusted based on the accepted surface area of the head (1300 cm^2) and using Eq. D2-8. The next step is to add the hand wash values together to obtain a dose value that is representative of the entire replicate. Finally, the last step is to calculate a cumulative dermal dose value over the entire replicate as described in Eq. D2-9 for each test subject. Table D2-6 illustrates these calculations for a single test subject based on example data from Table D2-1 and additional data developed for the purposes of this example. Along with the calculation of total dermal dose levels, total inhalation doses must be calculated using Eq. D2-10 and a human inhalation rate (e.g., 29 Lpm is used for example purposes).

Table D2-5. Example Residue Recovery Correction Calculation

Line	**Upper Torso Dermal Exposure/ Whole Body Dosimeters (total μg/sample)**		**Dislodgeable Foliar Residue (μg/cm^2)**	
	Not Corrected For Recovery[a]	**Corrected For Recovery**[b]	**Not Corrected For Recovery**[a]	**Corrected For Recovery**[b]
1	15.0	19.9	0.8400	0.9882
2	205	244	0.6500	0.7647
3	NQ	5.0	NQ	0.0025
4	1236	1236	0.5800	0.6824
5	115	137	0.6000	0.7059
6	19.0	25.2	N/A	N/A
7	550	550	N/A	N/A
8	89.0	106	N/A	N/A
9	ND	1.0	N/A	N/A
10	55.0	65.5	N/A	N/A
11	68.0	81.0	N/A	N/A
12	601	601	N/A	N/A
13	428	510	N/A	N/A
14	292	348	N/A	N/A
15	19.0	25.2	N/A	N/A

[a] All data included in this table are excerpted from Table D2-1.

[b] In this example, the recovery correction factor is the field recovery mean value for fortification level as these data are stipulated to serve as field recovery, concurrent laboratory recovery, and storage stability (i.e., they were stored and analyzed concurrently with the field samples in the example). The factors used to correct sample residue levels were calculated as illustrated in Table D2-2. Values at "ND" or "NQ" are not corrected.

Table D2-6. Example Exposure and Dose Calculations for Day 2 Reentry[a]

Line Number	Whole Body Dosimeter Residue Levels			Handwash Residue Levels			Dermal Patch Data (Head Exposure)		Total Potential Dermal Dose[d]	Internal Dose From Dermal Route[e]	Unit Dose Levels From Dermal Route[f]		Inhalation Data[g]		Total Internal Unit Dose[h]
	Lower Torso (µg)	Upper Torso (µg)	Total[b] (µg)	Wash #1 (µg)	Wash #2 (µg)	Total[b] (µg)	Patch Residue (µg)	Potential Dose[c] (µg)	(mg)	(mg)	Potential Dose (mg/hr)	Internal Dose (mg/hr)	Monitored [Air] (µg/m^3)	Inhalation Unit Dose (mg/hr)	(mg/hr)
1	25.0	19.9	44.9	200.0	120.0	320.0	15.0	97.5	0.462	0.069	0.116	0.017	22.3	0.039	0.056
2	125.0	244.0	369.0	150.0	459.0	609.0	10.0	65.0	1.043	0.156	0.261	0.039	25.0	0.044	0.083
3	11.0	5.0	16.0	125.0	67.0	192.0	11.0	71.5	0.280	0.042	0.070	0.011	9.7	0.017	0.028
4	756.0	1236.0	1992	400.0	325.0	725.0	8.0	52.0	2.769	0.415	0.692	0.104	17.1	0.030	0.134
5	159.0	136.9	295.9	300.0	150.0	450.0	9.0	58.5	0.804	0.121	0.201	0.030	19.6	0.034	0.064
6	30.0	25.2	55.2	280.0	890.0	1170.0	15.0	97.5	1.323	0.198	0.331	0.050	12.0	0.021	0.071
7	408.0	550.0	958.0	1200.0	230.0	1430.0	20.0	130.0	2.518	0.378	0.630	0.095	11.0	0.019	0.114
8	125.0	105.9	230.9	123.0	451.0	574.0	21.0	136.5	0.941	0.141	0.235	0.035	13.0	0.023	0.058
9	18.0	1.0	19.0	200.0	879.0	1079.0	5.0	32.5	1.131	0.170	0.283	0.042	10.0	0.017	0.059
10	75.0	65.5	140.5	700.0	123.0	823.0	13.0	84.5	1.048	0.157	0.262	0.039	8.6	0.015	0.054
11	38.0	81.0	119.0	560.0	485.0	1045.0	14.0	91.0	1.255	0.188	0.314	0.047	9.8	0.017	0.064
12	789.0	601.0	1390	483.0	683.0	1166.0	20.0	130.0	2.686	0.403	0.672	0.101	15.8	0.027	0.128
13	423.0	509.5	932.5	1100.0	453.0	1553.0	9.0	58.5	2.544	0.382	0.636	0.095	14.3	0.025	0.120
14	250.0	347.6	597.6	1050.0	234.0	1284.0	8.0	52.0	1.934	0.290	0.484	0.073	17.7	0.031	0.104
15	32.0	25.2	57.2	243.0	782.0	1025.0	11.0	71.5	1.154	0.173	0.289	0.043	21.0	0.037	0.080

Footnotes For Table D2-6:

a All data presented in this table are corrected for recovery (see Tables D2-1 and D2-5 for upper torso residue levels). All other dermal data were developed for the purposes of this table. Inhalation data included in lines 1 through 5 are excerpted from Table D2-4. All other inhalation data were developed for the purposes of this table. All handwash data were developed for the purposes of this table.

b Whole body dosimeter and handwash total (μg) values were calculated using the guidance provided in Eq. D2-9 (e.g., lower torso + upper torso = total).

c Potential head dose (μg) value calculated using Eq. D2-8 as follows: Potential Head Dose (μg) = Patch Residue (μg/200 cm^2) * 1300 cm^2 Dermal Head Surface Area.

d Potential dermal dose (mg) calculated using Eq. D2-9 as follows: (Whole Body (μg) + Hand (μg) + Head (μg))*(1 mg/1000 μg).

e Internal dose from dermal exposure calculated using a dermal penetration factor of 15% and Eq. D2-14 as follows: Internal Dose (mg) = (Potential Dermal Dose (mg) * Penetration Factor (%))/100.

f Unit dose calculated using Eq. D2-15 as follows (replicate duration was 240 minutes or 4 hours): Unit value (mg/hour) = Dose (mg)/Replicate Duration (hours).

g Unit inhalation dose (100% of exposure assumed to be internal dose) calculated using Eq. D2-10 as follows (note first term completed in Table D2-4): Inhalation Unit Dose (mg/hour) = [Air] (μg/m^3) * Human Inhalation Rate (29 Liter/minute) * (1 mg/1000 μg) * (60 minutes/hour) * (1 m^3/1000 liters).

h Total internal unit dose calculated by adding internal unit doses from dermal and inhalation routes.

After total potential dose levels are calculated, the next step is to calculate internal dose levels if appropriate as determined by the nature of the most sensitive toxicological endpoint (e.g., if the endpoint is an oral or feeding study). The calculation of an internal dose level also requires an absorption factor that is a measure of penetration of a pesticide through a biological membrane or barrier. For the purposes of this example, two dermal toxicological endpoints will be used (i.e., short-term and chronic). The short-term endpoint that will be used for all scenarios is a 21 day dermal rat study while the chronic endpoint will be a cancer slope factor generated using an oral dose. The dermal absorption factor used for the chronic scenario will be 15 percent (i.e., internal dose must be calculated for the cancer endpoint scenario). In a vast majority of the cases, total inhalation potential dose is also treated as the internal inhalation dose due to a lack of adequate data to provide further resolution. Unless data are available to indicate otherwise, or a sampling regimen has been established to measure various particle sizes, further internal inhalation dose calculations are not required. Table D2-6 illustrates the calculation of internal dermal dose levels using Eq. D2-14.

Subsequent to the calculation of dose, the next step is to normalize these values by an appropriate factor to obtain a unit dose level. In most cases, as these are reentry exposure scenarios, the normalization factor will be based on the duration of the exposure monitoring period (e.g., hours spent harvesting or at play on residential turf). Table D2-6 also illustrates the calculation of these unit dose levels.

The final step in the dose calculations is the statistical summary of the dose data via basic manipulations (refer to Sections 2.2 and 2.4.4). Table D2-7 provides a summary of the example dose data.

2.9.5 Chemical Dissipation Kinetics

This section provides examples of characterizing chemical dissipation kinetics from environmental media. In this case, the example is based on a typical agricultural reentry scenario (i.e., the use of dislodgeable foliar residues). However, the same approaches can be used to assess chemical dissipation for any environmental media/residue sampling approach (e.g., residues measured from turf, hard indoor surfaces, and carpets). In this example, dislodgeable foliar residues (DFRs) were taken over a 35 day sampling period after a single application to characterize DFR dissipation patterns and to provide data to relate to human reentry exposure levels concurrently measured in order to define transfer coefficients. The approach most commonly used by the Agency is a pseudo-first order kinetics model (i.e., this example will only address this approach -- other approaches used by investigators should be discussed with the Agency).

Table D2-7. Summary Statistics for Example (Day 2) Exposure Data[a]

Dose Descriptor	**Dose Units**	**Exposure Statistics**					
		Arithmetic Mean[b]	**Geometric Mean**[b]	**σ^b**	**C.V.**[c]	**95% CI Upper Limit**[d]	**95% CI Lower Limit**[d]
Total Potential Dermal Dose	(mg/hour)	0.365	0.307	0.205	56.2	0.469	0.261
Internal Dose From Dermal Exposure	(mg/hour)	0.055	0.046	0.031	56.4	0.070	0.039
Inhalation Dose	(mg/hour)	0.026	0.025	0.009	34.6	0.031	0.022
Total Internal Dose	(mg/hour)	0.081	0.075	0.032	39.0	0.097	0.065

a Data summaries in this table are based on the data presented in Table D2-6.

b Mean and σ values calculated using routines provided in a handheld calculator.

c C.V. = coefficient of variation calculated as described in Eq. D2-1 (34.6 = (0.009/0.026)*100)

d 95% CI = 95% confidence interval lower/upper limits calculated as described in Eq. D2-2

$(0.261 = 0.365 - ((0.205 * 1.96) / \sqrt{15}))$

To evaluate the kinetics, a log linear regression of measured DFR concentration data versus time is conducted to predict environmental pesticide residue levels over the course of the entire sampling period (i.e., Eq. D2-16). Typically, the Agency uses a semilog regression approach for this effort (see Eq. D2-17). Table D2-8 presents sample data from all sampling intervals corrected for field recovery for use in the example. The Day 2 data are taken from Table D2-1. After the calculation of the linear regression, the Agency also calculates a half-life using the pseudo-first order model (Eq. D2-18). These calculations and a graphical interpretation of the data are presented in Table D2-9 and Figure D2-5.

2.9.6 Transfer Coefficients and Exposure Models

This section illustrates the calculation and use of transfer coefficients as presented in Section 2.6 *Transfer Coefficients and Exposure Models*. This section does not provide a discussion concerning the use of the exposure models included in section D.2.6 because the intent of this example is to provide users of Series 875 guidelines with guidance pertaining to the core elements and approaches required for calculations under these guidelines.

Transfer coefficients are used to predict postapplication (i.e., reentry) exposures from environmental chemical concentrations for specific human activities such as tree thinning or children at play on turf. Historically, the agency has used dermal transfer coefficients in conjunction with dislodgeable foliar residue levels to calculate dermal reentry exposures for agricultural workers. This example focuses on this same scenario, agricultural tree thinning. However, the same approaches/techniques can be used for any correct combination of transfer coefficient and environmental concentration (e.g., PUF roller and indoor reentry exposure on carpets).

Several approaches can be used to calculate and present chemical transfer coefficients. These approaches, presented in Section 2.6, include simple proportions and linear regressions. Additionally, that section includes normalization factors other than hours worked that can be used by investigators to present results.

This example will focus on the hours spent thinning orchards during each exposure replicate (i.e., 240 minutes for all dermal exposure replicates). The first step in calculating a transfer coefficient is to summarize the concurrently generated dislodgeable foliar residue and human reentry exposure data. The next step is to calculate the proportional relationship between the datasets. Example calculations of transfer coefficients, based on the example data used throughout this section, are presented in Table D2-10. These transfer coefficients were calculated using Eq. D2-19. All calculations in this table used arithmetic mean values.

Table D2-8. DFR Data To Be Used In Example Kinetics Calculations[a]

Sampling Interval (Days After Treatment)	DFR Levels (μg/cm²)					Statistical Summary of DFR Levels[b,c,d]			
	Replicate 1	Replicate 2	Replicate 3	Replicate 4	Replicate 5	Arithmetic Mean (μg/cm²)	Natural Log of Mean (μg/cm²)	Standard Deviation (μg/cm²)	Coefficient of Variation (%)
Pre-Application	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025	-5.9915	0.0000	0.00
0	1.1213	1.3201	1.2451	1.1894	1.2015	1.2155	0.1951	0.0734	6.04
1	1.0123	1.0584	1.0432	1.0324	1.0451	1.0383	0.0376	0.0172	1.66
2[a]	0.9882	0.7647	0.0025	0.6824	0.7059	0.6287	-0.4640	0.3704	58.91
4	0.5189	0.6543	0.5646	0.5648	0.4564	0.5518	-0.5946	0.0725	13.14
7	0.3712	0.3815	0.3620	0.3700	0.3501	0.3670	-1.0025	0.0117	3.19
10	0.2301	0.2295	0.2401	0.2314	0.2416	0.2345	-1.4501	0.0058	2.48
14	0.1120	0.1201	0.1098	0.1132	0.1140	0.1138	-2.1731	0.0039	3.38
21	0.0584	0.0464	0.0565	0.0496	0.0565	0.0534	-2.9296	0.0052	9.82
28	0.0214	0.0195	0.0156	0.0251	0.0165	0.0196	-3.9308	0.0038	19.58
35	0.0098	0.0056	0.0097	0.0089	0.0079	0.0084	-4.7819	0.0017	20.66

[a] Day 2 data excerpted from Table D2-5. All data in this table are considered corrected for field recovery.

[b] Mean and standard deviation calculated using all 5 datapoints for each day.

[c] Coefficient of variation calculated using the following equation: ((Std. Dev./Mean)*100)

[d] Natural log values calculated using the mean value for each sampling day.

Table D2-9. Summary DFR Kinetics Calculations[a]

Parameter	Value
Constant[b]	-0.003676
Std Err of Y Est	0.144582
R Squared	0.993597
No. of Observations	10
Degrees of Freedom	8
Correlation Coefficient	-0.996793
Slope (Eq. D2-17 M value)	-0.139813
Std Err of Coefficient	0.003968
Half Life (Days)[c]	4.96

[a] Values calculated using a commercial spreadsheet package based on a semilog regression using Eq. D2-17 of Ln[DFR($\mu g/cm^2$)] versus sampling interval (days after application).

[b] Predicted values presented in Figure D2-5 were calculated using Eq. D2-16 or $DFR_{Day\ 21} = DFR_{Day\ 0} * e^{(21\ days\ *\ (-0.139813))}$ where $DFR_{Day\ 21} = 0.0529\ \mu g/cm^2$ and $DFR_{Day\ 0} = e^{-0.003676} = 0.9963\ \mu g/cm^2$

[c] Half-life value calculated using Eq. D2-18 or ($t_{1/2} = 0.693/0.139813$)

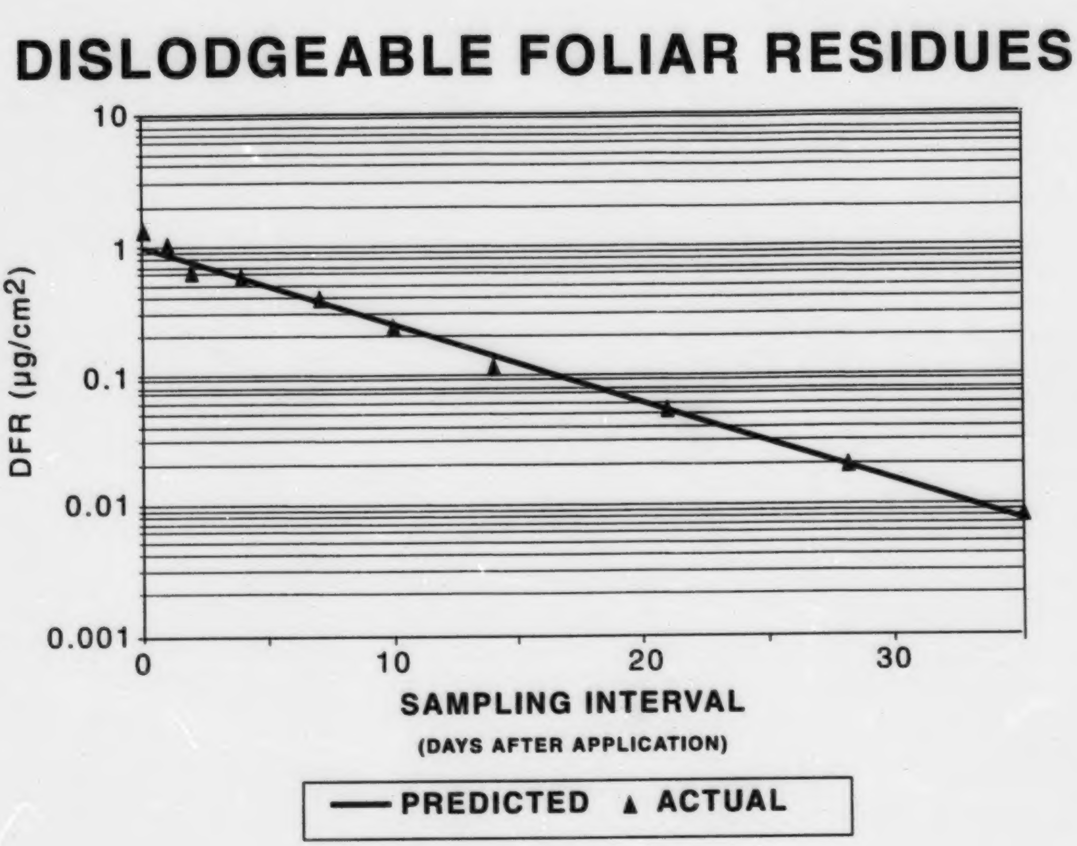


Figure D2-5. Example Chemical Dissipation Data

Table D2-10. Example Transfer Coefficient Calculations

Study Day	**[DFR][a] ($\mu g/cm^2$)**	**Unit Dermal Exposure[b] (mg/hour)**	**Transfer Coefficient[c] (cm^2/hour)**	**N (Exposure/DFR)**
1	1.0383	0.952	917	15/5
2	0.6287	0.365	580	15/5
4	0.5518	0.325	589	15/5
Mean	0.9991	0.547	695[d]	45/15

a Mean DFR levels have been developed throughout the entire example calculation process (e.g., refer to Tables D2-5 and D2-8). This value represents actual measured data corrected for field recovery. Some investigators believe the use of predicted DFR values are appropriate. Any submission to the Agency should clearly indicate which value was selected and a rationale for the selection. DFR levels for Days 1 and 4 have been developed for inclusion into this table.

b Unit dermal exposure levels for Day 2 are have been developed throughout the entire example calculation process (e.g., refer to Tables D2-6 and D2-7). Unit dermal exposure levels for Days 1 and 4 are included in this table with no previous references to them in this example.

c Transfer coefficients calculated using arithmetic mean values for both the DFR and dermal exposure values. Transfer coefficient calculated using Eq. D2-19 as follows (Day 2 provided as example):

$580\ cm^2/hour = ((0.365\ mg/hour)/((0.6287\ \mu g/cm^2)*(1\ mg/1000\ \mu g)))$

d There is discussion concerning the use of significant figures when presenting transfer coefficient values. Generally, the Agency believes the use of 1 or 2 significant figures is appropriate based on the uncertainties associated with the data used to calculate them. As a result, a transfer coefficient of 700 will be used in all example REI calculations (e.g., Table D2-12).

In order to calculate dose once activity specific transfer coefficients are known, investigators must use Eq. D2-20 (or some modification thereof if a linear regression as opposed to a proportion is used). Using the same data that are included in Table D2-10, calculation of an exposure on Day 2 can be completed using Day 2 DFR and the mean value transfer coefficient as follows:

$$0.440 \text{ mg/hour (dermal exposure)} = 0.6287 \ \mu g/cm^2 \text{ (Day 2 DFR)} * 700 \ cm^2/\text{hour (TC)} * (1 \text{ mg}/1000 \ \mu g)$$

Several issues must be considered in the use transfer coefficients. For example, in this instance the transfer coefficients presented in Table D2-10 were similar across each day of reentry (i.e., mean of 564 cm^2/hour with a C.V. over all three days of 6.2 percent). As a result, the transfer coefficient used in the example calculation was the mean value generated over all reentry exposure monitoring days (i.e., 1, 2, and 4 days after application in this example). However, in some cases variability in transfer coefficients may occur across time (i.e., the transfer coefficients seem to fluctuate with the DFR data). In those cases, investigators should consider using different transfer coefficients for the same activity depending upon the environmental concentration (e.g., DFR level).

2.9.7 Average Daily Dose (ADD) and Lifetime Average Daily Dose (LADD)

The next step in the calculation process is to develop average daily dose estimates for short-term toxicological endpoints and amortized lifetime average daily dose levels for chronic toxicological endpoints (i.e., cancer). In most cases (i.e., except for cancer endpoints), only the calculation of *Average Daily Dose* is required as described in Eq. D2-28. The key element in the application of this equation is to ensure that the adjustment factor (e.g., hours worked per day or hours engaged in a play activity per day) is the same as the factor used to normalize the unit dose value. It should be noted as well that calculation of the average daily dose can also be dependent upon the pattern of reentry days as exposures generally differ over time due to residue dissipation from treated surfaces.

The most common normalization factor used by the agency for postapplication exposure calculations is the duration engaged in the activity. Other factors that have also been used include worker productivity gauged by crops harvested (e.g., pounds per replicate) or acres covered (e.g., acres mowed). For this example, all calculations will be based on the hours worked during citrus tree thinning (8 hours per day is assumed by the agency in all calculations). Unit dermal dose values presented in Table D2-10 were used to calculate Average Daily Dose levels as illustrated in Table D2-11. Additionally, amortized dose levels for cancer endpoints calculated using Eq. D2-29 are illustrated in this table (e.g., a 70 year lifetime and 35 years per activity are assumed for this example).

Table D2-11. Example ADD and LADD Calculations

Study Day	ADD$_{pot}$ Calculation Parameters (for non-cancer dermal endpoint)			LADD$_{int}$ Calculation Parameters (for cancer endpoint)					
	Unit Potential Dermal Dose[a] (mg/hour)	**Hours Worked Per Day**	**ADD$_{pot}$[b,c]** (mg/kg/day)	**Unit Internal Dose[a]** (mg/hour)	**Hours Worked Per Day**	**Average Lifetime** (years)	**Exposure Duration** (days/year)	**Exposure Duration** (years)	**LADD$_{int}$[b,d]** (mg/kg/day)
1	0.952	8	0.109	0.152	8	70	45	35	1.01 x 10
2	0.365	8	0.042	0.055	8	70	45	35	3.87 x 10
4	0.325	8	0.037	0.051	8	70	45	35	3.59 x 10
Mean	0.547	8	0.063	0.086	8	70	45	35	6.06 x 10

a Unit dermal dose values excerpted from Table D2-10. Unit internal dose values excerpted from Table D2-7 (Day 2) and developed for example purposes for this table (Days 1 and 4).

b All calculations completed using a body weight of 70 kg.

c ADD$_{pot}$ calculated as follows using Eq. D2-28, 8 hours per day, and a body weight of 70 kg as follows:
0.109 (mg/kg/day) = (0.952 (mg/hour) * 8 (hours/day))/70 kg body weight

d LADD$_{int}$ calculated as follows using Eqs. D2-28 and D2-29, ADD parameters (i.e., 8 hour day and 70 kg body weight) and amortization parameters (i.e., 45 days/year exposure, 35 working years, and 70 year lifetime). The ADD calculation is an interim step not included as a table column. Example calculations for study day 2 are as follows:

ADD$_{int}$ or 6.28×10^{-3} (mg/kg/day) = (0.055 (mg/hour) * 8 (hours/day))/70 kg body weight; and
LADD$_{int}$ or 3.87×10^{-4} (mg/kg/day) = 6.28×10^{-3} (mg/kg/day) * (45 (days/yr)/365 (days/yr)) * (35 years exposure/70 year lifetime)

2.9.8 Risks, Hazards, and Restricted Entry Intervals

The Agency typically regulates pesticides by calculating *Margin of Exposure* (MOE) or cancer risks as illustrated in Eqs. D2-30 and D2-31. Example calculations have been developed that illustrate one approach for calculating postapplication risks for a *Restricted Entry Interval (REI)*. It should be noted that there are several different ways to complete these dose/risk calculations (e.g., predicted versus actual dose or predicted versus actual DFR values). The method used here is for illustrative purposes only. An example has been completed for short-term and cancer endpoints for the REI scenario and for the short-term endpoint in the non-REI scenario. These examples are included in Table D2-12. In this example, the mean value transfer coefficient for citrus tree thinning is used in all examples. Using this transfer coefficient value and predicted DFR levels, cancer risks and short-term MOEs were calculated. As indicated in Table D2-12, the REI is 5 days for citrus tree thinning based on the 21 day dermal rat study and the REI is 20 days based on the cancer endpoint.

EXPOSURE PARAMETERS	
DAILY WORK INTERVAL (hrs/day):	8
BODY WEIGHT (kg):	70
EXPOSURE FREQUENCY (days worked/year):	45
EXPOSURE DURATION (years worked):	35
LIFETIME (anticipated lifetime -- years):	70
TRANSFER COEFFICIENT (cm2/HOUR):	700

TOXICOLOGY PARAMETERS	
DERMAL PENETRATION FACTOR (%):	15
21 DAY DERMAL ENDPOINT (mg/kg/day):	10
CANCER SLOPE FACTOR (1/(mg/kg/day)):	0.01
SHORT-TERM MOE SAFETY FACTOR (EQN. D2-29):	100

DAT	PREDICTED DISLODGEABLE FOLIAR RESIDUES (ug/cm2)	UNIT POTENTIAL DOSE (mg/hour)	UNIT INTERNAL DOSE (mg/hour)	AVERAGE DAILY POTENTIAL DOSE (mg/kg/day)	AVERAGE DAILY INTERNAL DOSE (mg/kg/day)	LIFETIME AVERAGE DAILY INTERNAL DOSE (mg/kg/day)	SHORT TERM REI CALCULATION		CANCER RISK REI CALCULATION	
							MARGIN OF EXPOSURE	IS REENTRY ACCEPTABLE?	CANCER RISK	IS REENTRY ACCEPTABLE?
0	0.9963	0.6974	0.1046	0.0797	1.20e-02	7.37e-04	125	YES	7.37e-06	NO
1	0.8663	0.6064	0.0910	0.0693	1.04e-02	6.41e-04	144	YES	6.41e-06	NO
2	0.7533	0.5273	0.0791	0.0603	9.04e-03	5.57e-04	166	YES	5.57e-06	NO
3	0.6550	0.4585	0.0688	0.0524	7.86e-03	4.85e-04	191	YES	4.85e-06	NO
4	0.5695	0.3987	0.0598	0.0456	6.83e-03	4.21e-04	219	YES	4.21e-06	NO
5	0.4952	0.3467	0.0520	0.0396	5.94e-03	3.66e-04	252	YES	3.66e-06	NO
6	0.4306	0.3014	0.0452	0.0344	5.17e-03	3.19e-04	290	YES	3.19e-06	NO
7	0.3744	0.2621	0.0393	0.0300	4.49e-03	2.77e-04	334	YES	2.77e-06	NO
8	0.3256	0.2279	0.0342	0.0260	3.91e-03	2.41e-04	384	YES	2.41e-06	NO
9	0.2831	0.1982	0.0297	0.0226	3.40e-03	2.09e-04	442	YES	2.09e-06	NO
10	0.2462	0.1723	0.0258	0.0197	2.95e-03	1.82e-04	508	YES	1.82e-06	NO
11	0.2140	0.1498	0.0225	0.0171	2.57e-03	1.58e-04	584	YES	1.58e-06	NO
12	0.1861	0.1303	0.0195	0.0149	2.23e-03	1.38e-04	672	YES	1.38e-06	NO
13	0.1618	0.1133	0.0170	0.0129	1.94e-03	1.20e-04	772	YES	1.20e-06	NO
14	0.1407	0.0985	0.0148	0.0113	1.69e-03	1.04e-04	888	YES	1.04e-06	NO
15	0.1224	0.0856	0.0128	0.0098	1.47e-03	9.05e-05	1022	YES	9.05e-07	YES
16	0.1064	0.0745	0.0112	0.0085	1.28e-03	7.87e-05	1175	YES	7.87e-07	YES
17	0.0925	0.0648	0.0097	0.0074	1.11e-03	6.84e-05	1351	YES	6.84e-07	YES
18	0.0804	0.0563	0.0084	0.0064	9.65e-04	5.95e-05	1554	YES	5.95e-07	YES
19	0.0699	0.0490	0.0073	0.0056	8.39e-04	5.17e-05	1787	YES	5.17e-07	YES
20	0.0608	0.0426	0.0064	0.0049	7.30e-04	4.50e-05	2055	YES	4.50e-07	YES
21	0.0529	0.0370	0.0056	0.0042	6.35e-04	3.91e-05	2364	YES	3.91e-07	YES

NOTES:

- + PREDICTED DFR VALUES BASED ON KINETICS DATA PRESENTED IN TABLE D2-9 AND FIGURE D2-5.
- + NOMENCLATURE FOR ALL VALUES CONSISTENT WITH TABLES D2-1 THROUGH D2-11.
- + ACCEPTABLE MOE FOR THIS CALCULATION IS 100 (i.e., EQN. D2-29 SAFETY FACTOR).
- + ACCEPTABLE RISK FOR THIS CALCULATION IS 1E-6.

Table D2-12. Example REI Calculations

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PART D - CHAPTER 3

MODELING D3-1

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PART D - CHAPTER 3
MODELING

3.1 INTRODUCTION

Models can be used for risk assessment in the absence of empirical data, as a supplement to limited data, or to mathematically describe complex exposure situations. The use of predictive models may be required in the course of estimating human post-application exposures to pesticides to address data gaps as it is not always possible to collect adequate test data to fully address each scenario of concern. For example, the dilution and dissipation of chemicals in indoor air over time may be modeled or the dissipation rates of chemicals may be predicted based on physical-chemical properties. Additionally, modeling approaches may be required even when empirical data are available because of the complex nature of the postapplication risk assessment or the nature of the calculations required to adequately utilize the power of the available data. For example, attempting to account for the multiple potential activity and behavioral patterns that occur in a residential setting (e.g., time, location, and behavioral data inputs). The use of models potentially also has several other benefits including completing risk assessments early in the product development process, alleviating, in some cases, the need for conducting expensive and complex human exposure studies, and as tools for developing risk-based product support or enforcement policy approaches (e.g., develop relative risk rankings for chemical classes).

Generally, models transform known inputs or conditions into an exposure/risk analysis using mathematical algorithms created to predict an output for the given scenario. The mathematical algorithms that serve as the basis for models generally fit into two distinct categories including those that can predict chemical characteristics in the environment based on physical/chemical properties, and those that describe the treatment of existing data. Examples of predictive approaches based on the physical/chemical characteristics of a chemical would be the calculation of emission rates using molecular weight and vapor pressure or predicting environmental behavior (i.e., fate and transport) based on the principle of fugacity. Conversely, algorithms that describe the treatment of existing data could include sampling from a data distribution for stochastic modeling or development of an activity pattern scenario for a residential assessment based on a compilation of existing data.

Although models can be powerful tools for the risk assessment process. Assessors should be careful to abide by a "good modeling practice" approach and consider the level of validation as well as other risk characterization issues associated with any model that has been utilized to address an exposure scenario. Assessors should include discussions of risk characterization issues during the calculation process and more importantly while interpreting the results of an assessment. The "good modeling practice" approach essentially mirrors the basic tenets of the Good Laboratory Practices (40CFR160) in that all assessments completed using a model should be mathematically transparent and reproducible by reviewers. Additionally, the rationale pertaining to how decisions regarding data inputs and the use of empirical data were made should be clear from any assessment. The level of validation of any selected model is a primary risk characterization issue for the Agency. Available information pertaining to the development and validation of the selected model should be included (at least in summary form) in any assessment as this will provide insight into the regulatory importance that should be associated to the assessment. Additionally, a discussion of the appropriateness of the model should also include several other risk characterization issues including a discussion of the anticipated levels of accuracy and precision, a discussion of the reliability of the inputs, and a discussion of any other critical issues that should be considered in the interpretation of the assessment. Assessors should also abide by other general requirements of the exposure assessment process including compliance with the U.S. EPA Exposure Assessment Guidelines (see Part D-Chapters 1 and 2 for further information).

This chapter provides a discussion of some of the parameters involved in modeling exposure to chemicals and an overview of some of the models that may be applicable to estimating postapplication exposure to chemicals. This chapter also provides more specific guidance on generally-accepted model validation criteria and recommendations on presenting an exposure assessment completed using a model. The intent of this chapter is not to provide an in-depth discussion of all of the models or issues that may be used to exhaustively address postapplication exposure issues. Such an in-depth analysis is left to each assessor, given the numbers and variety of the assessments that are anticipated by the Agency in response to Food Quality Protection Act requirements for chemicals in the residential marketplace and to address exposure issues related to those occupationally exposed in the agricultural and industrial/commercial marketplaces.

3.2 MODELING PARAMETERS

Modeling parameters can be divided into two categories: those that pertain to the estimation of the chemical concentration in a localized environment, and those that pertain to the estimation of individual exposure in an environment. This discussion of modeling parameters focuses on indoor air concentrations because, currently, modeling is most frequently used by EPA to estimate indoor air concentrations of pesticides (e.g., after the use of antimicrobials and after indoor crack-and-crevice application).

3.2.1 Estimation of Chemical Concentration

The concentration of a particular chemical in an indoor environment can be estimated by examining the chemical of concern and the environment in which it exists. Properties of interest are: the physical and chemical properties of the chemical of concern, the properties of the environment in which the chemical exists. For example, for an indoor environment, information about the environmental chamber (house), the airflow throughout the environmental chamber, and the effects of sources and sinks in the environment is needed. These parameters are generally inputs into the model and are, in some cases, essential for running the model.

One element of determining the concentration of a chemical in an environment is evaluating the physical and chemical properties of the chemical of concern. In general, a mass balance equation is used to determine the amount of the chemical present. The amount of chemical present is equal to the amount that was placed in the system minus the amount that has left the system. For example, the amount of pesticide remaining after application to a room is equal to the amount initially applied minus the amount that has dissipated. The remaining pesticide is in two forms: the liquid portion that has not evaporated, and the vapor portion that lingers in the air. Chemical properties—such as volatility, reactivity, and the ability of a chemical to decay and produce other chemicals—can be used to determine how much, if any, of the chemical has evaporated into the surrounding air. Knowing the amount of the chemical in the ambient air, the amount of the chemical remaining on the applied surface, and the airflow through the chamber, one can determine, using the mass balance equation, the amount of chemical present, which in turn can be related to an exposure concentration (CMA, 1993).

A second environmental property of consideration is the environment in which the chemical exists. In assessing indoor air concentrations, the characteristics of the environmental chamber, or house, being studied is of interest. The environmental chamber can consist of one room or many rooms. The size, or volume, of the environmental chambers is important in helping to determine the ratio of the vapor concentration of the chemical of concern to the amount of air available. Large or multi-roomed chambers may afford a larger volume of air in which to dilute hazardous vapors. The ambient temperature and pressure of the environmental chamber will also affect the amount of chemical released into the vapor phase, and where it may be located. The structural elements of a room, such as the placement of doors, windows, and stairs, also affect how chemical vapors will flow through a room and where these vapors may condense to form dermal hazards. All of these factors need to be considered when selecting and using a model (Austin et al., 1992).

Other factors that shape the environment being analyzed are fate and transport parameters. For indoor air, this can include the airflow in the environmental chamber and the occurrence of sources and sinks. The airflow assists in the evaporation of a chemical as well as its transport into and out of the environmental chamber. Airflow can be a function of changes in temperature and pressure. It can also be the result of mechanical turbulence (e.g., a fan or air conditioner). As mentioned above, the structural factors of an environmental chamber can affect the transport of vapors throughout a room. Pockets of chemical vapors could occur in corners or spaces throughout a room due to lack of airflow. If an environmental chamber has multiple rooms or is one large room, airflow characteristics may cause a gradient in vapor concentrations throughout the chamber. Therefore, it is important to understand the properties of the airflow (e.g., the velocity, direction, etc.) in an environmental chamber in order to ensure proper performance of the model (Austin et al., 1992; CMA, 1993).

Sources can be described as physical objects that release a chemical into the environment. Sinks, on the other hand, can be considered objects that trap, or remove, a chemical from the environment. The ability of these objects to affect the mass balance of a particular chemical is dependent on the physical, as well as the chemical, makeup of the objects. Source emission rates are used to provide information on how much of a particular chemical will be released into the air at given periods of time. The surface area, as well as the relative location of a source or sink, may be used in a model to determine the amount of a chemical that may pose a dermal threat (Austin et al., 1992; CMA, 1993).

3.2.2 Estimation of Human Exposure

Human exposure to a chemical can be estimated by defining those factors that pertain to the chemical of concern and the individual being exposed. The properties pertaining to the chemical of concern have already been discussed. The properties defining the exposed individual include the following: the exposed population, the exposure duration, the exposed individual's activity patterns, and the exposure routes.

The exposed population is the set of individuals being exposed to chemicals in the environmental chamber. The exposed population can be described by parameters such as age, sex, race, and occupation. Such parameters will help shape decisions on exposure duration and exposure route parameters described below. For example, an infant may be exposed to a chemical in a much different fashion than an elderly person. At the same time, a housewife may be exposed to a chemical for a much longer time than a woman who works at an office and is only exposed to the room for a few hours. Exposed populations may or may not be put directly into a computer model.

Exposure duration is how long an individual is exposed in an environmental chamber. This can be measured in hours per day, days per week, days per year, and so forth. This parameter will help determine the acute or short-term exposures, and the chronic or long-term exposures. This parameter is usually put into computer models.

Activity patterns are what an individual does in the environmental chamber. The patterns are directly related to the amount of the chemical to which an individual will come into contact. An individual sitting and watching television does not respire as rapidly as an individual who is exercising, and, therefore, will not inhale the same amount of a chemical in the air. However, if the chair of the person sitting is treated with the chemical of concern, the person sitting and watching television may be exposed dermally to the chemical of concern, while the exercising person is not. In addition, activity pattern data help to define the placement of an individual within the treated area relative to chemical concentrations in the environmental chamber. For example, for individuals residing in a home where pesticides have been applied in the basement, postapplication exposures may be the highest during activities conducted in the basement and lower when activities are performed in other parts of the house. Activity patterns may or may not be a direct input parameter for exposure models (Austin et al., 1992).

The last property considered in estimating human exposure is the exposure route of the chemical. The exposure route indicates how the chemical comes in contact with an individual. For the purposes of this discussion, inhalation, dermal contact, and ingestion are the exposure routes being considered.

3.3 EXAMPLES OF COMPUTER MODELS

Described below are two indoor air quality models, one dermal model, and a migration model that are currently used by EPA to estimate potential chemical exposure. These models were selected for discussion because they have been accepted and are currently supported by the EPA's Office of Pollution Prevention and Toxics (OPPT) for assessing new and existing chemicals. Additional, exemplary exposure-related models and software products that may be appropriate for assessing postapplication exposure to pesticides are briefly described in Appendix 3-A to this chapter. This appendix is not a comprehensive list and the mention of model and software names is not an endorsement. However, the Appendix provides a sampling of products that may have utility for postapplication exposure assessments. It is left to the reader to determine the appropriate model and software of choice for a given situation and to document the modeling approach and appropriate validation. Additional software systems, exposure-related databases and online systems are addressed by U.S. EPA (1992) and P.J. Hakkinen (1997).

Multi-Chamber Concentration and Exposure Model (MCCEM)

Description:

MCCEM is an interactive model developed for the EPA's, OPPT and updated for the Office of Research and Development (ORD) by Geomet Technologies, Inc. The model is used for assessing inhalation exposure to airborne concentrations of chemicals released from products in residences. It contains a database of house data needed to run an indoor air model—information such as air exchange rates, inter-room airflows, and house and room volumes. The user can enter source emission rates of pollutants into the model either as numbers or as formulas. MCCEM accounts for chemical decay and changing outdoor concentrations over time. It is capable of performing sensitivity analyses and Monte Carlo analyses (U.S. EPA, 1991).

Input parameters:

The following are input parameters for MCCEM: environmental chamber location, type of environmental chamber, geographic location, exposure duration, the number of exposures per year, the number of years of exposure, room size, pollutant concentration in outdoor air, inter-room airflow rates, emission rates, decay rates, chemical levels of concern, and the number of rooms being analyzed.

If the Monte Carlo analysis option is selected, the type of distribution and lower boundary of the distribution for the infiltration rate, source rate, decay rate, and outdoor concentration must also be provided.

MCCEM allows the user to explore the sensitivity of the model results to changes in one or more of the input parameters. If the sensitivity analysis option is selected, the multiplicative factor for the parameter of concern must be included. Parameters that can be modified in the sensitivity analysis include the infiltration rate, the source rate, the decay rate, and the outdoor concentration.

Default Values:

MCCEM provides default values for the input parameters discussed above. When calculating the Lifetime Average Daily Dose (LADD) values, MCCEM assumes a default breathing rate of 20 cubic meters per day, a default body weight of 70 kilograms, and default average lifetime of 70 years.

Output Parameters:

MCCEM provides summary statistics (average concentration, standard deviation, maximum concentration and the percent of the values above the level of concern) for a chemical in each room, the percent of time an individual is in the environmental chamber, and the estimated LADD.

Output Products:

MCCEM can summarize inputs and outputs on the computer monitor. ASCII text files and data files are also created to provide the user the opportunity to further review the data.

SCREENING CONSUMER INHALATION EXPOSURE SOFTWARE (SCIES)

Description:

SCIES has been developed for the EPA's OPPT by Versar Inc. The model is used to assist in performing screening-level assessments of potential dose rates from inhalation of new and existing chemicals in consumer products. The model classifies consumer products in 10 categories and estimates potential average individual dose rates from inhaling each component of a consumer product based on the product category in which it has been placed. The model estimates potential dose rates for both the user of the product and passively exposed non-users. The model allows for the selection of default consumer product categories as well as a user-input scenario (U.S. EPA, 1994). EPA is currently in the process of developing the Consumer and Occupational Model (COM), which will incorporate a consumer inhalation exposure module similar to SCIES and will eventually replace the SCIES model in performing screening level assessments for new and existing chemicals at OPPT.

Input parameters:

The following parameters are input into SCIES: chemical name (optional), molecular weight of the chemical, vapor pressure, weight fraction of the chemical, the room where the product was used, and user occupancy patterns. In the user-input scenario, the following parameters may also be required: the annual frequency of use, the mass of the product used per event, the air exchange rate, the non-user inhalation rate, the user inhalation rate, the duration of use, room volume, and the environmental chamber volume.

Default Values:

SCIES provides default values for all of the parameters listed above in the user-input scenario. SCIES uses a two-room environmental chamber (the room where the product was released and the rest of the environmental chamber) and assumes the concentration of the product outside the environmental chamber is zero. Product use is restricted to rooms labelled "the kitchen" or "the bedroom".

Output Parameters:

SCIES provides data on the annual potential dose rates for active- and passive-exposed individuals, evaporation time, the amount of time following each use of the product, the interval between uses of the product, the average and peak predicted concentrations in the two rooms for users and non-users, and a summary of the hourly activity patterns for users and non-users throughout the environmental chamber.

Output Products:

SCIES can summarize the inputs and outputs for a model run on the computer monitor or send the summary to a printer. A text file can also be created so that the file can be imported into a word processing program (e.g., WordPerfect).

DERMAL

Description:

DERMAL is a dermal exposure model developed for EPA's OPPT by Versar Inc. to be used in performing screening-level assessments of the potential dose rates from dermal contact with consumer products containing new and existing chemicals. The model allows the user to select from 1 of 16 consumer product categories for screening-level estimates. The model also allows users to design their own scenarios for products not included in the model. The model is user-friendly and requires minimum input from the user (U.S. EPA, 1995). OPPT's COM will include a dermal exposure assessment module that will update and replace the DERMAL model. COM is currently under development by OPPT.

Input parameters:

DERMAL requires the following input parameters: median and high-end weight fraction of chemical in product; median and high-end skin surface area exposed; film thickness of liquid on skin; density of the product; dilution fraction; low, median, and high-end frequency of events; and, low, median, and high-end years of use of the product in a lifetime. For certain consumer products, more information on the exposed portion of skin and the amount of product contacting the hands may be required.

Default Values:

Default values exist for all of the input parameters, except for the weight fraction inputs, for the 16 consumer product categories in the DERMAL model. These default values can be changed during any model run.

Output Parameters:

DERMAL outputs the central, high-end, and bounding acute potential dose rates, and the central and high-end LADD.

Output products:

DERMAL allows the user to send all of the input and output data results to the screen, to a printer, or to a WordPerfect file.

AMEM (Arthur D. Little Migration Estimation Model)

Description:

AMEM (U.S. EPA, 1990) is a computer program that facilitates the rapid estimation of the fraction of additives originally in polymer sheets that will migrate under various conditions. With AMEM, one can estimate migration of additives to fluid and solid external phases. The Exposure Evaluation Division of the Office of Pollution Prevention and Toxics at the EPA assesses the potential for exposure to chemicals that are used as additives in polymeric materials or are the monomers or low molecular weight oligomers contained in polymers, by using AMEM or similar models. AMEM, which also has subroutines that estimate many physical properties (diffusion coefficients of additives in the polymers, in air, and in water; partition coefficients; and mass transfer coefficients), is coded in FORTRAN for operation on PCs.

Input Parameters:

The input parameters for AMEM include polymer thickness (cm); external phase type (air, water, or solid), and duration over which migration occurs (hrs). The diffusion coefficient (cm^2/s) of the chemical is also needed, and can be estimated by the model if the molecular weight of the migrant (g/mole) is known and the polymer type (e.g., silicone rubber, polystyrene, etc.) is selected from the model's menu. If partitioning effects and mass transfer resistance are considered, the user may also need to provide information on the saturation concentration of the migrant in the polymer (g/cm^3), vapor pressure (for air phases) (torr), melt temperature (for water phases) (°C), surface length (cm), air or water flow velocity (cm/s), volume of external phase (m^3), and surface area of the polymer (cm^2).

Output Parameters:

The model provides information on the fraction of polymer migrated and the diffusion coefficient in the polymer (cm^2/s), if estimated. If partitioning effects and mass transfer resistance are considered, estimated partition coefficients and mass transfer coefficients will be provided.

3.4 VALIDATION OF PREDICTIVE PESTICIDE EXPOSURE MODELS

In general, predictive pesticide exposure models must be shown to produce results that reflect "real-world" data. It is not enough that a model developer put forward a model and state that it produces accurate real-world data simply because a model is based on detailed theoretical mathematical representations. Regulatory authorities have traditionally relied upon field studies, conducted in accordance with the appropriate guidelines, because the data generated by field studies are based upon measured concentrations. Although field study data may be limited in strength because the results may reflect only one specific location under one set of conditions, they can be considered valid for real-world conditions. Predictive models, in contrast, generate results that are based upon mathematical representations of physical, biological, and chemical processes. The confidence that regulatory authorities can place in predictive models is based upon the accuracy of the input parameters, and the degree to which the model has been proven to reproduce observed field-generated data. Thus, regulatory authorities require validation of predictive models through the generation of data that demonstrate that:

i) input variables are accurate and appropriate (which includes ensuring that the computer source code is properly debugged and that there is confirmation that the algorithms are mathematically correct), and

ii) results from predictive models are reliably comparable to those seen in field studies (i.e., "real world" data should be generated to confirm model output).

Field studies used for validation purposes must be representative of the various scenarios that a model may predict. Thus, it is not adequate to conduct a single validation study for a model that makes predictions for different types of formulations, hydrophobic and hydrophilic compounds, and various settings (e.g., single room vs. entire home). The validation data must reflect the various scenarios the model predicts.

In addition, validation studies must have been conducted using the same guidelines required for the conduct of the corresponding field studies (i.e., Series 875, Group B for residential pesticide exposure studies). Hence, issues such as the appropriate number of replicates and quality assurance are still of concern when validating a model. Validation studies that are not conducted according to the required regulatory guidelines for field studies cannot be considered valid in themselves and, as such, cannot be used to validate predictive models.

3.5 REPORTING CRITERIA FOR MODEL-BASED ASSESSMENTS

The reporting of all assessments should be based on the principles and requirements described in the *Data Reporting Guidelines* that have been developed for this document. These guidelines are presented in Appendix I. Assessors should also review and incorporate the general guidance pertaining to the exposure and risk assessment process that is described in Chapters 1 and 2 of Part D of this document (i.e., Chapter 1: Fundamentals of Exposure and Risk Assessment and Chapter 2: Calculations), and *The International Harmonization Position Paper: Guidelines For Using and Reporting PHED Data* (Final Draft of 9/19/1997).

Critical issues and requirements that are specific to reporting model-based assessments are summarized and presented below. These include:

- Providing an adequate description of the model used in the assessment including source, version number, and operational requirements (e.g., Windows or DOS-based).
- Providing an adequate description of the model inputs along with a description of any assumptions used.
- Developing risk characterization language that describes and quantifies the uncertainties associated with model inputs, model validation, the model algorithm, and for interpreting the resulting risk assessment.
- Providing a working copy of the model(s) used to accompany any exposure/risk assessment.
- Including all model inputs/outputs in any submission (e.g., hardcopy of input tables and outputs).

APPENDIX 3-A: EXPOSURE MODELS/SOFTWARE BIBLIOGRAPHY

The following paragraphs briefly discuss additional models and software products that may be relevant for assessing postapplication pesticide exposure or factors (e.g., physical/chemical properties) necessary for estimating these exposures. The products' capabilities and computer requirements, as well as available contacts are included. The list is not intended to be inclusive of all available models and software, but provides a sampling of products with potential utility for postapplication exposure assessments.

AERIS (Aid for Evaluating the Redevelopment of Industrial Sites)

AERIS is a soil toxicity model developed by SENES Consultants Ltd., Ontario, Canada. The model, which is specifically designed to meet the soil testing requirements for the Decommissioning Steering Committee in Canada, provides estimates of concentrations of chemicals in contaminated soil that are used to help establish cleanup guidelines or to indicate when remedial actions are required. Model inputs include site-specific data, physical and chemical properties, transport calculation methods, and exposure parameters. The model also estimates human exposures resulting from contaminated soil. The PC-based model includes a lookup database that contains physical and chemical properties of certain chemicals.

API DSS (American Petroleum Institute Decision Support System)

API DSS estimates exposure concentrations and subsequent risk from a suite of fate and transport models coupled with toxicity parameters. Relevant exposure pathways evaluated by the models include vapor intrusion (from soil) into homes, volatilized chemicals from bathroom showers, soil ingestion, and ingestion of food and water.

CalTOX (California Toxicity Model)

The Department of Toxic Substances Control (DTSC) of the California Environmental Protection Agency has the responsibility for managing the state's hazardous waste program. As part of this program, the DTSC funded the development of the CalTOX program (McKone, 1993a, 1993b, 1993c). CalTOX has been developed as a set of spreadsheet models and spreadsheet data sets to assist in assessing human exposures and defining soil cleanup levels at uncontrolled hazardous waste sites. CalTOX addresses contaminated soils and the contamination of adjacent air, surface water, sediments, and groundwater. The modeling components of CalTOX include a multimedia transport and transformation model, exposure scenario models, and add-ins to quantify uncertainty and variability. The multimedia transport and transformation model is a dynamic model that can be used to assess time-varying concentrations of contaminants introduced initially to soil layers or for contaminants released continuously to air, soil, or water. This model assists the user in examining how chemical and landscape properties impact both the ultimate route and quantity of human contact. Multimedia, multiple pathway exposure models are used in CalTOX to estimate average daily doses within a human population. The exposure models encompass 23 exposure pathways. The exposure assessment process consists of relating contaminant concentrations in the multimedia model compartments to contaminant concentrations in the media with which a human population has contact (personal air, tap water, foods, household dust, soils and so forth.

CHEMCAN

CHEMCAN, which is similar to CalTOX and USES, is a multiple media fugacity model designed to estimate the distribution of single chemicals in multiple media. Given emission rates and chemical properties, it estimates chemical concentrations in air, food, soil, and water. CHEMCAN was developed for Environment Canada.

CONSEXPO (CONSumer EXPOsure Model)

CONSEXPO (Van Veen, 1995) is a modeling approach based on simple exposure and uptake models. In order to cope with the diversity in consumer products, it is based on a model framework that provides a general setting for widely differing exposure situations. It also offers a number of predefined exposure and uptake models, which users can link to build a complete exposure and uptake model. The starting points are the inhalation, dermal, and ingestion exposure pathways. For each of these pathways, a limited number of models are available for exposure and uptake. The program reports several important exposure variables; namely, the per-event concentration, the yearly averaged concentration, the fraction taken up, the amount taken up during a year (per year and summed), and the uptake per kilogram of body weight per day. The program also allows for stochastic parameters, in order to propagate the effects of variable and/or uncertain parameters to the final exposure and uptake estimates. If stochastic parameters are included, the resulting distributions can be displayed and studied.

The CONSEXPO program is related to the USES programs (also discussed in this section). CONSEXPO can be operated as a stand-alone program or as part of the framework of USES. The computer system requirements for CONSEXPO are an Intel-based PC, Microsoft Windows 3.1, and at least 1 MB of available hard drive space. A math coprocessor is not mandatory, but is highly recommended.

CONTAMx

The National Institute of Standards and Technology (NIST) has, over the past several years, developed a series of public domain computer programs (CONTAM86, CONTAM87, CONTAM94) for calculating airflow and contaminant dispersal in multiple zone buildings. These programs take a multiple zone network approach to airflow analysis. Airflow paths include doorways, small cracks in the building envelope, and a simple model of the air handling system.

CONTAM94, the most recent version of CONTAMx, works on an Intel-based PC in the DOS environment. A graphical interface is used to create and edit building descriptions. Future versions of this program will include exposure assessment.

EASE (Estimation and Assessment of Substance Exposure)

The EASE system was developed by the United Kingdom Health and Safety Executive in conjunction with the Artificial Intelligence Applications Institute. EASE is a knowledge-based system that stores knowledge on specialized subjects along with the reasons for that knowledge. EASE estimates exposure of workers to notified substances. Particularly, it estimates inhalation exposure to dust and vapor and dermal exposure.

EML/IMES (Exposure Models Library/Integrated Model Evaluation System)

EML, developed by the EPA's Office of Research and Development, is a collection of exposure models distributed in a CD-ROM (U.S. EPA, 1996). The purpose of this disc is to provide a compact and efficient means for distributing exposure models, documentation, and the IMES. The disc contains over 120 models that may be used for transport modeling and exposure assessments. The model files may contain source and/or executable code, sample input, and other data files, sample output files, and, in many cases, model documentation in WordPerfect, ASCII text, or similar formats. IMES assists in selecting appropriate models, provides literature citations on model validations, and demonstrates model uncertainty protocols. The IMES software is an MS-DOS application, can be used on an Intel-based PC, and is capable of running on a network. Model codes and documentation can be downloaded from the CD-ROM to a hard drive. The most recent version, which is the third edition, has an HTML interface to view model directories and an internet source for some models.

For copies of the CD or for technical assistance, the contact person is Richard Walentowicz at the EPA's Office of Research and Development in Washington, D.C. (phone: 202-260-8922, E-mail: walentowicz.rich@epamail.epa.gov).

INDOOR/EXPOSURE/RISK (IAQ Model for Windows, RISK Version 1.0)

RISK is the third in a series of indoor air quality models developed by the Indoor Air/Radon Mitigation Branches of EPA's National Risk Management Research Laboratory. The first model, INDOOR, was designed to calculate the indoor pollutant concentrations from indoor sources. The second model, EXPOSURE, extended INDOOR to allow calculation of individual exposure. RISK extends EXPOSURE to allow analysis of individual risk to indoor pollutant sources. Risk estimates generated by models such as this one are useful mainly for the purpose of comparing scenarios rather than for determining absolute risks to individuals or populations.

RISK uses data on source emissions, room-to-room airflows, air exchange with the outdoors, and indoor sinks to predict concentration-time profiles for all the rooms. The concentration-time profiles are then combined with individual activity patterns to estimate exposure. Risk is calculated using a risk calculation framework. The model allows analysis of the effects of air cleaners located in the central air circulating system and/or individual rooms on Internal Air Quality (IAQ) and exposure. The model allows simulation of a wide range of sources, including long-term steady state sources, on/off sources, and decaying sources. Several sources are allowed in each room. The model allows the analysis of the effects of sinks and sink re-emissions on IAQ. The results of test house experiments were compared with model predictions. The agreement between predicted concentration-time profiles and the test house data was good. The model is designed to run in the Windows operating environment.

RISK can be ordered from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161 (Phone: 703-487-4650). The complete report is titled "IAQ Model for Windows, RISK Version 1.0: User Manual," (Order No. PB96-501 929).

MMSOILS (Multiple Media Soil Model)

MMSOILS estimates the human exposure and health risk associated with releases of contamination from hazardous waste sites. It is a multimedia model addressing the transport of a chemical in groundwater, surface water, soil erosion, the atmosphere, and accumulation in food. The human exposure pathways considered in the methodology include: soil ingestion, air inhalation of volatiles and particulates, dermal contact, ingestion of drinking water, consumption of fish, consumption of plants grown on contaminated soil, and consumption of animals grazing on contaminated pasture. For multimedia exposures, the methodology provides estimates of human exposure through individual pathways and combined exposure through all pathways considered. The risk associated with the total exposure dose is calculated based on chemical-specific toxicity data.

The methodology is intended to be used as a screening tool. It is critical that the results are interpreted in the appropriate framework. The intended use of the exposure assessment tool is for screening and relative comparison of different waste sites, remediation activities, and hazard evaluation.

The methodology can be used to provide an estimate of health risks for a specific site, but the uncertainty of the estimated risk may be quite large (depending on the site characteristics and available data), and this uncertainty must be considered in any decision-making process.

MMSOILS was developed to operate on an Intel-based PC. Other minimum system requirements are 512 KB of available random access memory, one 3-1/2" or 5-1/4" floppy disk drive, one hard disk drive (2.0 MB storage available), and DOS 3.x or higher. Because of the extensive computations involved in MMSOILS, it will operate most effectively on a 386 or 486 series computer equipped with a math coprocessor.

PC-GEMS (Personal Computer - Graphical Exposure Modeling System)

GEMS supports exposure and risk assessments by providing access to single medium and multimedia fate and exposure models, physical and chemical properties estimation techniques, statistical analysis, graphics and mapping programs with related data on environments, sources, receptors, and populations. Under development since 1981, GEMS provides analysts with an interactive, easily learned interface to various models, programs, and data needed for exposure and risk assessments on the EPA's NCC VAX cluster. PC-GEMS is a stand-alone version of GEMS that can be run on a PC.

The environmental models in GEMS are atmospheric, surface water, land unsaturated (soil) and saturated (groundwater) zones, and multimedia in nature. Methods for estimating octanol-water partition and adsorption coefficients, bioconcentration factor, water solubility, melting and boiling point, vapor pressure, Henry's constant, acid dissociation constant, lake/stream volatilization rate, and atmospheric half-life are available. Data sets are related to environmental characteristics (climate, soil, rivers, groundwater, vegetation), source releases (POTWs and industrial water discharges, Census business patterns, RCRA permit sites), and receptors (population and household estimates for 1970, '80, '90, and '95 by small area census district; drinking water facilities). Mapping routines in GEMS support Tektronix 4014 and color 4105/06/25/35, and ASCII terminals or PCs. PC-GEMS supports Hercules, CGA, and EGA graphics.

PC-GEMS is available with air, surface water and groundwater models and associated environmental and 1980 population data encompassing most of the United States System requirements: IBM AT or compatible, Math Coprocessor (80187/80287/80387), 640K RAM, 20 Mb of dedicated disk space or Bernoulli cartridge.

RISKPRO

RISKPRO provides an integrated system that includes environmental modeling programs, site, and chemical tracking and supporting tools. Six programs are provided to simulate the transport and transformation of a chemical through air, water, and soil. The models interact with each other. Chemical property estimation and environmental databases are included.

RISKPRO is a compartmentalized system consisting of

(1) AUTOEST - a chemical property estimating program,
(2) ISCLT (Industrial Source Complex Long Term Model) - an air dispersion modeling program,
(3) PTPLU (Point Plume) - a single source Gaussian dispersion modeling program,
(4) SESOIL (Seasonal Soil Compartment Model) - a soil transport modeling program,
(5) AT123D - a groundwater transport modeling program, and
(6) EXAMS (Exposure Analysis Modeling System) - a surface water modeling program.

Also included within the system are several databases that include climate information for the United States, geographic information, census data, and a catalog of SMILES notations. RISKPRO was produced by General Sciences Corporation as an updated, user-friendly version of PCGEMS.

RISK*ASSISTANT

Developed by Hampshire Research Institute, RISK*ASSISTANT for Windows, a commercial product, provides a straightforward tool for evaluating complex risks, useful for both novice and professional risk assessors. The software provides information on hazard, exposure, and risk, and allows flexibility for tailoring the assessment to local sites. Risks from air, surface water, groundwater, soil, sediment, and food can be assessed. The software offers the choice of chemical and concentration data sets, alternative populations, exposure scenario factors, and toxicity data sets. Risks can be calculated for single scenarios (e.g., showering) or multiple scenarios (drinking water, showering, and eating local fish).

Sensitivity analyses can be performed to determine the effect of exposure variables on risk estimates. Transport models included are ISCLT2 (air dispersion model to predict chemical concentrations in the air surrounding points where toxic chemicals are released as air emissions) and STREAM (surface water model to predict the downstream concentrations of contaminants in rivers and streams). The software provides more than 15 MB of hydrology data on U.S. water bodies.

Databases in the software include hazard data for 650 chemicals. They provide EPA data on carcinogenic and noncarcinogenic toxicity, from the Integrated Risk Information System (IRIS) or Health Effects Assessment Summary Tables (HEAST). Other toxic hazard data bases can be easily incorporated.

SmartRISK

SmartRisk is a stand-alone commercial application designed for conducting human health risk assessments. Calculations follow the EPA paradigm: Hazard Identification, Exposure Assessment, Dose Assessment, Risk Characterization. Exposure is characterized through scenarios, and multiple pathways are considered. Exposure scenarios require exposure media contact, exposure durations, and exposure frequencies. All calculations are deterministic. Risk reports can be exported to a spreadsheet format in order to perform Monte Carlo Simulation using Crystal Ball or @RISK. For additional information, contact Pioneer Systems Development (phone: 206-822-4461; E-mail: pioneer@halcyon.com).

THERdbASE (Total Human Exposure Risk database and Advanced Simulation Environment)

THERdbASE is the result of a cooperative agreement with EPA's Office of Research and Development (National Exposure Research Laboratory, Las Vegas). THERdbASE is being developed as a PC-based computer modeling and database system that contains exposure- and risk-related information. The system provides an optimal framework for the construction of a suite of exposure- and risk-related models within the Modeling Engine by using information available in data files within the Database Engine.

Data can be viewed as a table, coded fields can be viewed as decoded fields, fields can be set to "show" or "hide" mode, and multiple data files can be viewed at the same time. In the "advanced" mode, user files can be edited. Data records can be queried and simple statistics (summary statistics: mean, standard deviation, minimum and maximum; percentile values at desired intervals; and linear regression on two numerical data fields) can be performed. Data can be printed, saved, or exported. New user files can be created and data can be imported.

Input to models is achieved through a standardized procedure. Inputs can be provided as single values, custom distributions (normal, lognormal, etc.), distributions based on data files present in THERdbASE, or specific percentile values. Efficient algorithms are provided to optimally access input data, to perform the numerical simulations, and to generate appropriate output data. Multiple model runs can be done through a batch process. Outputs from models are conducted as THERdbASE data files or as pre-set graphs.

In the Internet version of THERdbASE, the following data files are included:

- 1990 Bureau of Census Population Information
- California Adult Activity Pattern Study (1987-88)
- AT&T-sponsored National Activity Pattern Study (1985)
- 1992-94 National Human Activity Patterns Study (NHAPS)

- chemical agents from sources
- chemical agent properties
- air exchange rates
- information from EPA's TEAM (Total Exposure Assessment Methodology) studies
- information from EPA's NOPES (Non-Occupational Pesticides Exposure Study) studies
- human physiological parameters

In the Internet version of THERdbASE, the following models are included:

- location patterns
- chemical source release - instantaneous emission
- chemical source release - timed application
- indoor air (2-Zone)
- indoor air (N-Zone)
- exposure patterns for chemical agents
- Benzene Exposure Assessment Model (BEAM)
- source-based exposure scenario (inhalation + dermal)
- film thickness-based dermal dose
- PBPK-based dermal dose

The computer requirements of THERdbASE are an Intel-based 486 or higher PC, at least 8 MB of RAM, at least 40 MB of available disk space, a color VGA monitor, and Microsoft Windows 3.1. The most recent installable version of THERdbASE underwent beta-testing and a beta version is in the Internet (WWW site: http://www.hrcweb.lv-hrc.nevada.edu).

USES (Uniform System for the Evaluation of Substances) and EUSES (European USES)

USES (RIVM, 1994), was developed in the Netherlands by the National Institute of Public Health and Environmental Protection (RIVM); Ministry of Housing, Spatial Planning and Environment (VROM); and the Ministry of Welfare, health, and Cultural Affairs (WVC). USES provides a single framework for comparing the potential risks of different chemical substances released to multiple media of the environment. It is an integrated modeling system that includes multiple environmental media and multiple human exposure pathways. The exposure assessment in USES starts with an estimate of substance emissions to water, soil, and air during the various life-cycle stages of a substance and follows its subsequent distribution in the total environment. The results of this type of multi-media assessment are the Predicted Environmental Concentrations (PECs) and an estimate of the daily intake by human receptors. In general, PECs are compared to "no-effects" levels for organisms in the environment, which are derived by extrapolating single-species toxicity tests to field situations. The estimated daily intake by humans is compared to the "no-observed-adverse-effect" level for mammals or to the "no-effect" level for humans.

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APPENDIX I: DATA REPORTING GUIDELINES

APPENDIX I - DATA REPORTING GUIDELINES

I.1 INTRODUCTION

This Appendix provides a summary of the particular types and amounts of data that should be included in study reports. The types of data generated under Series 875, Group B include, but may not be limited to, the following:

- Pre-Field Data;
- Field Notes;
- Climatological Data;
- Characterization Data;
- Analytical Methodologies;
- Quality Control Data; and
- Residue Data/Results.

Critical data reporting requirements are discussed below. The Agency encourages investigators to provide data both electronically (e.g., standard commercially available spreadsheets such as Lotus, Quattro Pro, or Excel) and in hard copy. Data provided in electronic format may ease the Agency's review efforts by eliminating the data entry step and, therefore, may expedite the reregistration process. Where possible, each specific datapoint should be entered as an individual piece of information (i.e., individual cell in a spreadsheet).

I.2 DATA REQUIREMENTS

I.2.1 Pre-field Data

Any data that are critical to the design and implementation of a study must be reported in any submission to the Agency. Pre-field data may include the following:

- Detailed Product Use Information;
- Reentry/Postapplication Human Activity Pattern Information;
- Environmental Fate and Transport Data;
- Product Chemistry Data;
- Toxicity Data;
- Sampling and Analytical Methodology;
- Dosimeter Selection Criteria;

- Dosimeter Preparation Data;
- Crop/Crop Group Selection Criteria;
- Site Selection Criteria; and
- Application Selection Criteria.

In general, the types of data described above will not require significant manipulation prior to use by the Agency. A succinct narrative that summarizes the data should be provided along with the raw data (e.g., product use information, fate and transport data, product chemistry data, toxicity data, and analytical methodology). Any data used as a reference in this section (e.g., fate and transport data, product chemistry data, toxicity data) that have been submitted to the Agency for other reregistration purposes must be clearly identified by the appropriate Agency coding system (e.g., Master Record Identification (MRID) Number).

I.2.2 Field Notes

Field notes are a critical component to the successful completion of any study. Field notes should describe, in detail, all activities that occur during the field phase of a study. Field notes may include information pertaining to the following:

- Study Site Description and Map;
- Lot/Batch Numbers for Test Substance;
- Description of Individual Test Subjects (e.g., height, weight, years of experience, name, etc.);
- Exposure Monitoring Interval (i.e., time of day, duration, etc.);
- Timing of Dislodgeable Residue Sampling and Exposure Monitoring;
- Calibration Data for Application Equipment and Monitoring Devices;
- Field Recovery Sample Descriptions;
- Descriptions of Dosimeters, Personal Clothing and Protective Clothing/Equipment;
- Observations on Work Practices;
- Sample Locations in a Treated Area;
- Description of Sampling Equipment;
- Sample Storage and Shipment;
- Comments not Described in the Fields Above; and
- Any Protocol Deviations.

Several types of data included in the list above may be reported electronically as well as in hard copy. Map/site descriptions should be as detailed as possible. All data collected that are specific to each test subject may also be reported in electronic format (e.g., exposure interval, personal monitoring pump calibration data, lot/batch number of end-use-product, and clothing/dosimeter scenario).

I.2.3 Climatological Data

Climatological data should be reported for the entire study period. They may be collected on-site using appropriate instruments, or the data may be acquired from a variety of offsite sources. Most instruments currently used by investigators are not capable of generating data in an electronic format (e.g., the only way to retrieve the data is to read a meter and record the datapoint in a log book). Also, data retrieved from offsite sources such as NOAA (National Oceanic and Atmospheric Administration), may not be available electronically. However, climatological data may be reported in electronic format, if possible. Such data may include the following:

- Wind speed and direction;
- Solar Radiation;
- Temperature (Air);
- Relative Humidity;
- Description of Weather Events and Irrigation Practices, including measurement of daily rainfall and total rainfall during the study period;
- Residential Practices (e.g., HVAC Set Points and Window Use);
- Industrial/Commercial Practices (e.g., Greenhouse Fan/Shade Cloth and Ventilation Practices); and
- Specific Descriptions of Monitoring Equipment.

Means, medians, and ranges for all appropriate data fields should be calculated and submitted (e.g., temperature and relative humidity over specific exposure intervals and/or study days).

I.2.4 Characterization Data

Characterization data may be supplied by investigators for the test substance, study soils, and water samples. Characterization of the test substance is a requirement of the Good Laboratory Practices (GLPs). Unless a significant number of lot/batches are used in a specific study, electronic reporting of this data is not required. This is also true for soil and water characterization data unless a significant number of sites are utilized in a study. Typically, test substance characterization data include a description of the analytical procedure, raw data (e.g., chromatograms), and the results. Soil and water characterization data usually include several parameters (e.g., texture, pH, etc.).

I.2.5 Analytical Methodologies

Analytical methodologies should be developed and validated according to the guidance included in Series 875, Group B and Residue Chemistry Methods 860.1340, and PR Notice 96-1. All results should be reported on the basis of sample matrix. For each matrix, the following summaries of the raw data must be provided:

- Description of the analytical methodology;
- Quantification and detection limits for all matrices and how each value was determined;
- Means for all samples;
- Standard deviations (σ) for all samples;
- Number of replicates per calculation (n) and reason(s) for excluding any datapoints;
- Coefficients of variation (C.V.) for all samples; and
- 95 percent confidence interval (upper and lower limits) at a minimum over all fortification levels.

I.2.6 Quality Control Data

Historically, the most common study deficiency that resulted in rejection of post-application exposure studies has been the lack of adequate quality control data. Various types of quality control data have been previously defined in this document. These data include, but are not limited to, the following: field recovery, laboratory recovery, storage stability, and travel spikes. (See Part C, QA/QC for overview and Figure C-1 for explanations of the various types of data.) The following summary statistics (Part D, Chapter 2) must be reported for individual sample matrices/types for each of the following types of quality control data (i.e., field recovery, laboratory recovery, storage stability):

- Means for all samples;
- Standard deviations (σ) for all samples;
- Number of replicates per calculation (n) and reason(s) for excluding any datapoints;
- Coefficients of variation for all samples; and
- 95 percent confidence interval (upper and lower limits) over all fortification levels.

Exclusion of any datapoint from these statistical summaries must be reported and justified (i.e., chain-of-custody problem or extraction/analysis problem). All quality control data should be reported in electronic format and in hard copy. Each individual datapoint must be identified.

I.2.7 Residue Data

Data contained in post-application exposure studies can represent one of two types of residues including: (1) environmental matrix levels such as found in soil or foliar samples, and (2) dosimeter levels such as found in a whole-body dosimeters or filters used for inhalation monitoring.

Typically, environmental matrix data are presented as individual replicate sample results collected at specific intervals after application. All such data should be reported as individual datapoints and not just means at each sampling interval. Residue levels should be presented on a $\mu g/cm^2$ basis where appropriate (e.g., foliar dislodgeable residue levels on a double-sided leaf where a single 1-inch diameter disc represents 10 cm^2 of surface area). Soil residue levels should be presented on a ppm basis (i.e., $\mu g/g$ soil).

Human exposure monitoring data are complex and may take many forms, depending upon the study design. Most investigators will usually opt to use passive dosimetry techniques for monitoring human exposure levels concurrent to the collection of environmental samples. [Note: For this reason, the discussion here will focus on the use of passive dosimetry. See the environmental matrix description in Part B, Chapter 10 for a discussion of biological monitoring data/results.] Typically, passive dosimetry data are presented as three distinct types of results, identified as the following:

- Dermal exposure (nonhand);
- Dermal exposure (hand); and
- Inhalation exposure.

Dermal (nonhand) exposure levels may be presented in a variety of fashions, depending upon the design of the study (i.e., which types of dosimeter are used). If the Durham and Wolfe patch technique is used, all raw data should be presented on a body sample location basis as $\mu g/cm^2$. If whole body-dosimetry is used in the study, all data should be reported either as: (1) total μg/sample, or (2) $\mu g/cm^2$, where the surface used to calculate the residue level is based on the unit surface areas for representative body parts as presented in Part D, Chapter 2. Dermal (hand) exposure levels should be presented as total μg/sample. Data for hand exposure monitoring samples can be reported for both hands combined or for each individual hand. Additionally, hand exposure results should be reported in a way that represents cumulative exposure over the course of an exposure monitoring interval (e.g., if hand samples were collected prior to lunch and at the end of a work day and if the dermal (nonhand) samples were collected only at the end of an exposure interval).

Inhalation data should to be reported in a slightly different format because of the nature of the monitoring techniques. The following types of data are typically required to calculate inhalation exposure levels:

- Residue levels presented as total residues in a sample (μg/sample);
- Flow rates (Lpm) when personal monitoring pumps are used for sampling (initial, final and mean values); and
- Conversion calculations for passive monitors, if used (e.g., equations for 3M™-type monitors).

I.2.8 Other Critical Considerations

The following issues must be reported in any submission to the Agency:

- Compliance with PR 86-5 (Standard Format for Data Submitted Under FIFRA and Certain Provisions of the FFDCA);
- Compliance with GLPs, specifically protocol amendments and deviations; and
- A statement of adherence to the FIFRA GLP standards.

I.3 EXPOSURE/RISK CALCULATIONS

The required types of calculations/parameters include: (1) residue dissipation kinetics; (2) determination of the proper exposure scenario based on detailed product use and activity pattern data; (3) exposure estimates (potential and internal); (4) relationship between activity, ambient residue levels, and exposure (e.g., transfer coefficients); and (5) the regulatory implications of these calculations (e.g., development of Restricted Entry Intervals and product use restrictions and/or cancellations). See Part D, Chapter 2 - Calculations for a description of the calculations required.

1.4 DISCUSSION AND INTERPRETATION OF RESULTS

This section provides the submitter the opportunity to present a discussion and interpretation of the results. It should include a discussion of all assumptions used in the exposure calculations. Results should be discussed in terms of uncertainty and variability associated with the data. Detailed discussions may be needed for specific factors affecting the exposure estimate. Examples of these types of factors may include regional variations in HVAC system usage, or regional differences in cultural crop practices. Other uncertainties may include those associated with the nature of the population (i.e., based on age, gender, inherent variability, etc.).